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CANNABIS and Health Hazards

PROCEEDINGS OF AN ARF/WHO SCIENTIFIC MEETING ON ADVERSE HEALTH AND BEHAVIORAL CONSEQUENCES OF CANNABIS USE

Edited by Kevin O'Brien Fehr and Harold Kalant

ADDICTION
RESEARCH
FOUNDATION

Toronto, Canada, 1983

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Foreword

In the first quarter of this century, when the nonmedical use of cannabis was made illegal in Canada and the United States, this action was based in part on the commonly held view that cannabis was a highly dangerous drug that rapidly produced disastrous effects on the physical and mental health of its users. This belief was not substantiated by the careful but limited studies conducted by the Mayor's Committee in New York, in 1944. Cannabis was not widely used in occidental society at that time, and the Mayor's Committee Report[1] had only a limited impact on society at large. However, when marihuana began to be used by large numbers of white, middle-class, young Americans nearly twenty years ago, that report and the much earlier report of the Indian Hemp Drugs Commission[2] were frequently cited, by advocates of cannabis use, as evidence that the drug was harmless and should therefore be made legally available.

It is self-evident that any drug that is widely used nonmedically cannot be rapidly and dangerously toxic or lethal, or it would not be widely used. On the other hand, it is equally obvious that no pharmacologically active substance can be totally safe, since high enough doses will result in excessive effect that is, by definition, adverse. Therefore, medical and scientific "common sense" would lead one to expect that cannabis, like any other drug, is capable of causing *some* deleterious effects; that, like alcohol and tobacco, it may cause such effects slowly, as a result of chronic exposure to increasing doses; and that many years of clinical observation may be necessary before the full range, severity, and frequency of such effects can be assessed.

In 1981, the Addiction Research Foundation of Ontario, in collaboration with the World Health Organization, organized a Scientific Meeting in Toronto, Canada, to assess the evidence on adverse effects of cannabis that had accumulated up to that time. For this purpose, experts were invited from twelve countries in North and South America, Europe, Africa and Asia, and representing most of the relevant clinical and basic science disciplines. Thirteen of the participants prepared long critical reviews of the evidence concerning the various organ systems and functions in which most of the reported adverse effects had occurred. They were asked to assess the adequacy and validity of the evidence, point out its limitations and gaps, and attempt to reach such conclusions as the evidence permitted. The reviews were discussed intensively, and sometimes heatedly, during the week-long meeting, and a consensus was reached that formed the basis of an official report. The report was published in December, 1981[3], and is reprinted as the first chapter of this volume. It contains a summary of the evidence that was discussed at the

ARF/WHO Scientific Meeting, but it follows the format and practice of WHO reports and does not include the detailed critical reviews that formed the working papers.

By coincidence, two other expert committees were convened during the same year, to carry out essentially the same task. One was created by the Institute of Medicine, National Academy of Sciences (U.S.A.), and the other by the Advisory Council on the Misuse of Drugs (U.K.). The reports of both committees were published early in 1982[4,5]. As pointed out elsewhere[6], the three reports arrived independently at essentially similar conclusions, with some minor differences of emphasis and disagreements on a few specific points. In general, the conclusions were that cannabis is clearly *capable* of causing adverse effects on health, that some of these have already been recognized clinically in heavy users, that others have been produced in experimental animals but do not necessarily occur in humans at the dose levels that have been employed by voluntary users until now, and that there is a serious lack of systematic epidemiological information about the incidence and prevalence of such effects in different parts of the world, as a function of the extent of cannabis use in those regions.

The disagreements among the three reports reflect differences in the importance given by the three committees to clinical observation versus experimental proof, as well as differences in their respective estimates of the probability of future clinical occurrence of effects which have so far been reported only in experimental animals. In view of these different interpretations, we believe that basic and clinical scientists will want to be able to read and assess the evidence for themselves, and draw their own conclusions about the significance and clinical relevance of drug effects which are possible but not yet proven. The present volume is intended to give them a convenient opportunity to do so.

It consists of the detailed working papers for the Toronto meeting, updated and corrected by the authors, and edited only with respect to format, style, and verification of references. Unlike the American and British reports, which dealt essentially with actual or potential problems within their own countries, the present volume offers a perspective gained from observations (or lack of them) in Third World countries as well as in Europe and North America. It also contains a detailed consideration (especially in the chapter by Dr. H. Rosenkrantz, and the report of the ARF/WHO meeting) of the relation between cannabis doses used in experimental animals and those consumed voluntarily by humans for nonmedical purposes. This is a very important question, because assessment of the clinical relevance of effects seen in animal experiments depends in large measure on the degree of probability that humans may, or do, use equivalent doses.

The questions asked by the three committees cannot yet be answered definitively, but we now have a much clearer picture of what we know and what we do not know, and of what types of additional evidence are needed to permit valid answers. We hope the present volume will help to stimulate the research required to furnish those answers.

The editors and authors are greatly indebted to Mrs. Deborah Lindholm for her meticulous typing of the manuscripts, to Ms. Lise Anglin for skilled and thorough copy editing and proofreading, to Ms. Anglin and Mrs. Sylvia Lambert for preparing the indexes, and to Ms. Lia Hatashita, Ms. Barbara Fulton and Mr. Donald Murray for supervising the production of the finished volume.

Addiction Research Foundation HAROLD KALANT

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Report of an ARF/WHO Scientific Meeting on Adverse Health and Behavioral Consequences of Cannabis Use
Toronto, Canada,
30 March–3 April, 1981

1. INTRODUCTION

Background and Objectives

The report of a WHO Scientific Group on the Use of Cannabis,[1] which was published in 1971, brought together all the available information on the behavioral effects of cannabis use and other useful material. However, despite the existence of a substantial number of clinical case reports, not much accurate quantitative knowledge was available concerning the possible adverse effects of heavy use of cannabis on the health of users. Since that time, the extent of cannabis use in many countries has increased greatly, and a large body of experimental and clinical observations is now available. At the same time, a number of countries are re-examining their legal policies with respect to cannabis control, and require accurate knowledge on cannabis-related health hazards, as one element in their policy discussions.

In 1980–81, a joint study was undertaken by the Addiction Research Foundation (WHO Collaborating Centre) and the World Health Organization on "Adverse Health and Behavioral Consequences of Cannabis Use." A meeting of experts on various aspects of cannabis and health was convened in Toronto, Canada, from 30 March to 3 April, 1981,[2] under the joint auspices of the Addiction Research Foundation (ARF) of Ontario (Canada) and the World Health Organization, to undertake a critical assessment of current knowledge concerning the possible health hazards related to the use of this drug. The mandate extended to the participants was to consider only the scientific, clinical, and epidemiological information concerning potential and actual hazards to health resulting from the nonmedical use of cannabis and its various psychoactive constituents. The objectives were to review the evidence, assess its completeness and validity, identify significant points of disagreement or gaps in knowledge, and make recommendations with respect to research policy and specific matters requiring further research.[3]

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[1] In this report, the term "cannabis" refers to all preparations derived from the leaves, bracts, flowers, or resin of the plant *Cannabis sativa* L.
[2] See Appendix A for the list of the participants
See Appendix B for the list of the members of the planning committee

The present report has been submitted jointly by the ARF and WHO to the United Nations and other international bodies and agencies, national bodies, professional and educational groups, and others interested in the prevention and treatment of health problems related to the use of cannabis and other psychoactive drugs. It is anticipated that this information will constitute an important element in the deliberations of national bodies responsible for decisions on social and political policy with respect to drug use. However, such policy decisions are based on many other considerations—legal, political, social, ethical, and others—in addition to health concerns. Therefore, in the interests of effective and objective scientific discussion, the subject of control policies and policy recommendations was specifically excluded from the scope of this meeting.

In addition, it was decided not to consider the therapeutic uses or other beneficial effects of cannabis. This decision is in no way due to a rejection of the possibility of any beneficial or therapeutic effects, but arises from simple recognition of the fact that the evaluation of these effects is not directly related to the evaluation of the health hazards. Inclusion of the former would have enlarged the scope of the meeting beyond the limits of feasibility for the available time and the number of participants. An independent review, conducted by the Institute of Medicine, National Academy of Sciences, Washington, D.C., U.S.A. (1982), draws attention to the question of therapeutic uses and of other matters outside the scope of the present report.

Also in the interests of feasibility, this report does not deal with many basic scientific aspects of the mechanisms of action of cannabis. Such matters as the details of biotransformation, effects on cell membranes, neurotransmitter biosynthesis and turnover, electrophysiological processes, and experimental analysis of behavior are covered only to a very limited extent. The emphasis is on those basic processes and functional alterations which, on the basis of present knowledge, can be related directly to significant malfunction or disease in experimental animals or humans.

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[3] Complete referencing is not included in this summary because it can be found in the individual papers in this volume.

Definitions

Certain terms in this report have been used in the past in various ways. For the present purposes, the following explanatory comments are given.

"Adverse Effect"

An adverse effect of cannabis use may be considered to occur when such use produces impairment of an individual's biological, behavioral, or social function. Some effects (such as severe respiratory complications) would certainly be considered adverse in or by all users. However, it is clear that others (such as alterations of time sense), may be regarded as pleasurable or unpleasant, or as wanted or unwanted, according to circumstances and factors such as age, expectations, setting, or the perceptions and value systems of subjects or observers. Mental effects that are enjoyed by a young user at a party might be considered adverse by a middle-aged patient receiving a cannabis preparation in combination with cancer chemotherapy. A state which a student may describe as "agreeable relaxation" might be considered by the teacher as "impaired concentration." Reduction of blood pressure has been regarded both as a desirable therapeutic goal and as potentially dangerous. From this it is obvious that often no sharp classifications can be made, and the implications of such a phrase as "adverse effect" must be drawn from the context of its use.

"Intoxication" vs "Toxicity"

A similar situation applies to the judgment of toxicity. One person's "intoxication" is another person's "toxic reaction." There is a continuous spectrum, which exists also with alcohol and other drugs, and to draw any sharp line is necessarily arbitrary. The decision as to when to draw such a line is shaped by the user's own perceptions as well as by the observer's concern.

"Acute" vs "Chronic"

"Acute" is used to refer to single doses and their effects, or to reactions or responses on single occasions of brief duration. At the other extreme, "chronic" assumes various meanings. One of these refers to that duration of exposure beyond which further use reveals no new phenomena. Another meaning refers to a period of time that is a substantial fraction of the lifetime of a human or animal. It is worth noting that the pattern of dosage is important, and "chronic" effects may be evoked earlier with high than with low dose rates. Even when amount and pattern of alcohol consumption are allowed for, the latency of onset of Laennec's cirrhosis may range from 5 to 20 yr (Lelbach, 1974). Lung cancer from cigarette smoking, and carcinoma of the vagina following *in utero* exposure to diethylstilbestrol, also show long and variable latencies of onset. Therefore the production—and also the recognition—of some adverse effects of cannabis may require similarly long and variable periods of exposure.

Rates of Use

Words describing rates of use are particularly difficult to define. For example, the word "heavy" has been employed to describe use ranging from 1 g marihuana (or its equivalent) per week to more than 10 marihuana cigarettes (approximately 2–10 g) a day. Heavy use in one society may be perceived as light in another. The only satisfactory solution is to specify the use rates quantitatively, highlighting patterns of consumption, route of administration, and the potency of the material, as well as total amount used in unit time. Description of use as more or less "frequent" may sometimes be more appropriate than "heavy" or "light." Significant, too, may be particular details of self-administration; for instance, just as morning drinking of alcohol, or smoking immediately on rising in the morning, are signs of heavy consumption of alcohol and tobacco, so use of cannabis early in the day may be indicative of heavy consumption.

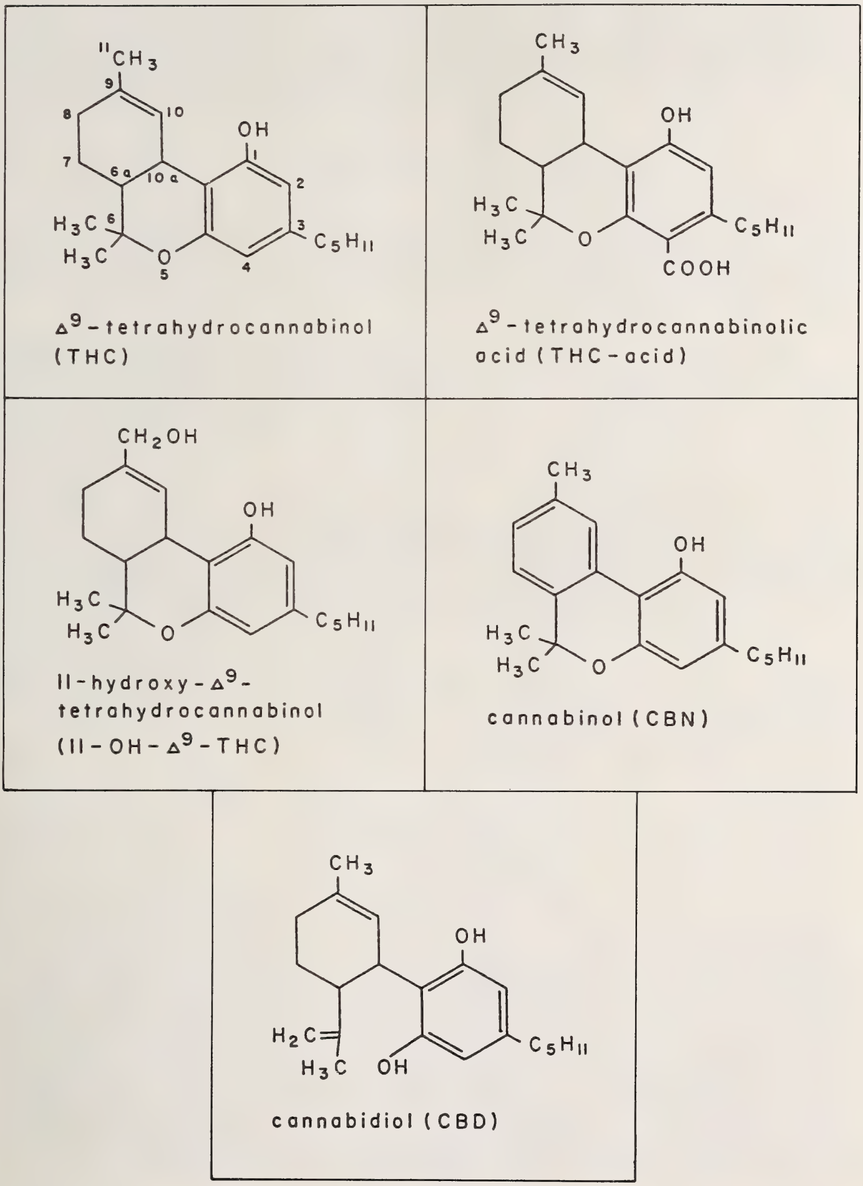
2. GENERAL TOXICITY

Cannabis Preparations

Among the 421 compounds thus far identified in the cannabis plant are approximately 61 with the cannabinoid structure (Turner *et al.*, 1980). Of the latter, (-) -Δ^9-tetrahydrocannabinol (THC) (Figure 1) is of greatest interest in the context of this report, since only structures closely related to THC elicit, at low doses, the characteristic mental effects that constitute the main reason for use of cannabis by humans (Mechoulam *et al.*, 1980). Several other cannabinoids including cannabidiol (CBD) and cannabinol (CBN) (Figure 1), as well as various noncannabinoid constituents of unpyrolyzed cannabis, may also have biological activities of other types. Dependent on the geographical origin of the plant, the relative and absolute contents of individual cannabinoids vary widely (Turner *et al.*, 1980).

Various preparations derived from the cannabis plant have a wide range of potencies. *Marihuana* or *bhang* consists mainly of dried leaves

FIGURE 1
Structures of Major Cannabinoids



$^{11}CH_3$
9
8
10
OH
1
7
6a
10a
2
H_3C
6
3
C_5H_{11}
H_3C
O
5
4
CH_3
OH
H_3C
H_3C
O
C_5H_{11}
COOH
CH_2OH
OH
H_3C
H_3C
O
C_5H_{11}
CH_3
OH
H_3C
H_3C
O
C_5H_{11}
CH_3
OH
H_2C
H_3C
OH
C_5H_{11}

Δ^9-tetrahydrocannabinol (THC)

Δ^9-tetrahydrocannabinolic acid (THC-acid)

11-hydroxy-Δ^9-tetrahydrocannabinol (11-OH-Δ^9-THC)

cannabinol (CBN)

cannabidiol (CBD)

and stems and can range in content from less than 1% to greater than 8% THC. The content of THC steadily decreases at a rate of approximately 5% per year in refrigerated plant material (Turner *et al.*, 1973). Other preparations *(hashish, ganja, charas)* made from the resin and flowering tops of the plant can contain up to 15% THC. Recently, solvent extracts of leaf material, flowers, or resin have appeared on the illicit markets. The potency of this so-called "hashish oil," "honey oil," or "weed oil" is extremely variable; the THC content can reach as high as 60%. The toxicity of these preparations appears to be related to their THC content, although other cannabinoids or noncannabinoids may contribute significantly. The biological effects of the remaining chemical constituents of these extracts are largely unknown at present. The existence of these high potency preparations facilitates the self-administration of large doses of THC.

The pyrolysis of cannabis products produces hundreds of compounds that make up the vapor and particulate phases of the smoke. The vapor phase consists of nitrogen oxides, carbon monoxide, hydrogen cyanide, and nitrosamines, together with other known toxic chemicals (Leuchtenberger, this volume). Along with the cannabinoids, the particulate phase contains many known carcinogens including phenols, cresols, and polynuclear aromatic hydrocarbons (Lee *et al.*, 1976). During pyrolysis at usual burning temperatures, tetrahydrocannabinolic acid (Figure 1) is activated by conversion to THC, but there appear to be few other significant cannabinoid interconversions. CBD can be converted to THC, especially when cannabis is pyrolyzed together with tobacco. About 50% of the total available THC is delivered in the mainstream smoke from a marihuana cigarette during the burning procedure (Rosenkrantz, this volume).

Lethality

Acute Studies in Experimental Animals

In acute studies, pure THC appears to be the most toxic cannabinoid of cannabis smoke. The LD_{50} values by inhalation and by i.v. administration are similar in rodents, and the LD_{50} for THC is smaller than those for CBD, cannabichromene, or crude marihuana extract. Intravenous LD_{50} values for THC range from about 40 mg/kg in the rat to 128 mg/kg in the monkey. In mammals, an interesting finding is that the potency of THC in lethality tests decreases as one ascends the phylogenetic tree. For most other effects, the potency is inversely related to the body size of the species, rats and mice being much more resistant than the Rhesus monkey or man (Rosenkrantz, this volume).

Species differences in pharmacokinetics must exist, since the ratio of the i.v. to the oral acute dosages ranges from about 1:30 to 1:40 for rodents but is closer to 1:100 for monkeys and probably dogs (Rosenkrantz, this volume).

In experimental animals, death usually results from cardiac arrest or respiratory failure. Since, at acute lethal doses, artificial respiration is only temporarily effective in preventing death, it appears that cardiac dysfunction rather than the profound hypopnea is the major cause of death (Rosenkrantz, this volume).

Chronic Studies in Experimental Animals

Chronic animal studies have indicated a significant degree of unexplained *delayed lethality.* In one experiment, approximately 12% of rats, mainly males, survived the initial dose but died suddenly after 2–3 wk of continued treatment (Rosenkrantz and Fleischman, 1979). Though the mechanism is not yet clear, it is possible that this delayed lethality may be related to accumulation of THC or its metabolites in the body during prolonged administration (see Section 9: Revelance of tissue sequestration to toxicity).

Humans

No LD_{50} values can be reliably estimated for humans, since only a very small number of fatalities have been reported, and the role of cannabis in these cases is questionable (Rosenkrantz, this volume).

Clinical and Experimental Toxicity

The past decade has witnessed the clinical documentation of many toxic effects that were previously described anecdotally or superficially. Systematic evaluations of clinical populations, closed-ward drug administration studies, controlled field studies, and accumulated self-reports by users have all been remarkably consistent in their findings. The more prominent effects are summarized below by organ system.

Respiratory Toxicity

Experimental animals. Single doses of cannabis or THC in animals affect respiration mainly by depression of respiratory rate. This effect is synergistic with that of general anesthetics and other central depressants. Though compliance (elasticity of lung and bronchioles) may be diminished, lung tissue damage has not been observed histologically in acute studies. However, prolonged and repeated exposure to cannabis smoke results in bronchiolar inflammation and morphological alteration of the lung in rats and dogs (Rosenkrantz, this volume).

Humans. Given acutely, THC or cannabis smoke produces a small transient respiratory depression (Bellville *et al.*, 1975) and bronchodilatation (Tashkin *et al.*, 1973).

Respiratory and pulmonary toxicity have emerged as major clinical complications of chronic cannabis smoking. Cannabis smoke appears to be more injurious to the lung than cigarette smoke, as judged by the use of sophisticated pulmonary function testing in well controlled studies (Rosenkrantz, this volume). Possibly because of its high combustion temperature, hashish appears to yield a particularly irritating smoke. In addition to the ability of cannabis to produce bronchitis, and obstructive pulmonary disease, it might after sufficient exposure produce cancer (see Section 3: Carcinogenicity). In the light of increased frequency of cannabis use, knowledge of the natural course of pulmonary disease suggests that the next three decades may demonstrate an increased prevalence of severe pulmonary disease and possibly of lung cancer. This risk is probably greater in those users (now a majority) who smoke cannabis and tobacco concurrently (Tennant, this volume). In present-day clinical settings the most commonly encountered toxic effects will be the respiratory problems of rhinitis, sinusitis, pharyngitis, and bronchitis (Tennant, this volume).

Cardiovascular Toxicity

Experimental animals. The major cardiovascular effects of a single dose of THC in most animal species are bradycardia, decreased cardiac reflexes, and hypotension. As a result, cardiac output and cerebral blood flow are usually decreased. Chronic administration may lead to some degree of tolerance to these effects (Rosenkrantz, this volume).

Humans. In humans, in contrast, the major effect of a single dose is tachycardia; the heart rate may reach 160 beats per minute or more (Hardman and Hosko, 1976). Acute effects on blood pressure, organ blood flow, and the EKG are variable and transient (Rosenkrantz, this volume; Tennant, this volume) and are probably due to varying degrees of effect on vasomotor tone (degree of constriction of blood vessels) and vasomotor reflexes (automatic responses to changes in body position, blood volume, etc.). In general, effects on supine blood pressure are relatively slight but postural hypotension has been repeatedly reported. There is little evidence of direct toxic effect on the heart muscle. Chronic use has not resulted in any detectable permanent alterations of cardiovascular function (Tennant, this volume). However, patients with preexisting heart disease due to a relative decrease in coronary blood flow may experience greater risk of angina pectoris and possible infarction because of the extra demand placed on the compromised heart by the drug-induced tachycardia (Tennant, this volume). Cannabis and tobacco smoke contain similar amounts of carbon monoxide. Therefore the formation of carboxyhemoglobin, which would also contribute to impaired oxygenation of the myocardium, also needs to be considered in cannabis smokers.

Growth and Body Weight

Experimental animals. Many studies have indicated that either single or repeated exposures to cannabis cause loss, or reduced rate of gain, of body weight (Rosenkrantz, this volume). This is probably due to both decreased food intake and altered endocrine function (see Sections 5 and 6). The long-term health consequences of growth impairment by these factors are unknown but may be most important in relation to the development of the fetus, neonate, or adolescent (see Section 6).

Humans. No data on body weight and growth rates before and during periods of cannabis use, comparable to those from controlled animal studies, are available for humans. Numerous clinical case reports from India and North Africa describe regular heavy cannabis smokers as emaciated or malnourished (Bouquet, 1951), and the observations of some modern field studies have suggested that regular users are lighter in weight than nonusers (Rubin and Comitas, 1975; Coggins *et al.*, 1980). Social factors such as marital status or other differences in life-style may have contributed to this finding (Coggins *et al.*, 1980). In short-term laboratory studies, a weight increase attributable to increases in body water and caloric intake has been observed (Jones and Benowitz, 1976; Greenberg *et al.*, 1976). There is little or no information on possible long-term effects of cannabis on growth, development, and maturation of humans.

Gastrointestinal

Experimental animals. In dogs and monkeys exposed to high oral doses of cannabis acutely, vomiting and diarrhea may occur (Thompson *et al.*, 1973). Chronic administration does not appear to be associated with significant gastrointestinal toxicity in animals (Rosenkrantz *et al.*, 1975), but may decrease gut motility.

Humans. In humans, acute or subacute use may produce vomiting, diarrhea, and abdominal distress (Halikas *et al.*, 1971; Tennant, 1974). Chronic cannabis use may decrease gastric acid secretion and possibly make the intestine more susceptible to *Vibrio cholerae* and *Escherichia coli* infections (Nalin *et al.*, 1978), which may pose a particular threat to travelers. Liver toxicity has been observed occasionally in cannabis users (Tennant, this volume). Concurrent alcohol abuse appears to be a factor in these cases. The mechanism by which cannabis could enhance alcohol-induced hepatotoxicity is unknown. The observation of abnormal liver function tests in users who had developed antibodies to marihuana (Shapiro *et al.*, 1976) suggests a possible antigenic response. Lysosomal damage, observed in animals treated chronically with THC (Mellors, 1976), may also play a role. The sharing of cannabis products or paraphernalia with other smokers has led to the spread of hepatitis in some groups (Drachler, 1975). Possible decreased immunity to viral infections is discussed in Section 4: Biological Significance.

Miscellaneous Toxic Manifestations

Individual case reports have also described a variety of apparent toxic reactions to cannabis in humans, of relative rarity and possibly dependent on unusual individual sensitivity (Tennant, this volume). For example, cannabis products often contain pathogenic fungi such as aspergillus, and aspergillosis has been reported to occur in cannabis-using persons who had pre-existing pulmonary disease or asthma (Kagen, 1981). Other allergic phenomena are often aggravated by cannabis use and one case of anaphylactic shock has occurred in an allergic person after cannabis use (Liskow *et al.*, 1971). Some clinical reports suggest that cannabis possibly aggravates some dermatological conditions (Tennant, this volume).

Toxicity Related to Unusual Methods of Cannabis Exposure

Unusual exposure to cannabis includes i.v. injection of plant extracts, oral ingestion of large amounts of the raw or cooked plant, swallowing of cannabis-filled balloons to escape police detection, and use of high-potency butter-paste preparations. The use of cannabis by the above routes has led to highly toxic reactions (Tennant, this volume). These reactions are either consequences of gross overdose (e.g., from intra-intestinal rupture of a balloon filled with "hash oil"), or complications produced by the physical rather than the pharmacological properties of the material (e.g., microembolism due to i.v. injection of a particulate suspension).

3. CELLULAR TOXICITY

Cytotoxic effects of cannabinoids have been studied by a number of different techniques, reflecting different research interests. The principal questions addressed include the possibility of cannabis mutagenicity, carcinogenicity, and impairment of biosynthesis of nucleic acids and proteins. These have involved both *in vivo* and *in vitro* approaches.

Chromosomal Aberrations and Mutagenicity

During the past 11 yr, about two dozen publications on the possible cytogenetic effects of cannabinoids have appeared (Bloch, this volume). Two-thirds have dealt with examination of human chromosomes, and the remainder with rodent chromosomes.

Cytogenetic analyses of lymphocyte cultures from chronic marihuana smokers have yielded contradictory results (Bloch, this volume). Four controlled prospective studies (Nichols *et al.*, 1974; Matsuyama *et al.*, 1976, 1977; Morishima *et al.*, 1979) involving experimental administration of 1 to 15 marihuana cigarettes a day for 5 to 13 days, gave no evidence of increased chromosomal breaks or gaps, though heavy doses gave rise to a higher proportion of hypoploid cells (i.e., cells containing a smaller than normal number of chromosomes) (Morishima *et al.*, 1979). This anomaly disappeared after cessation of smoking.

Rodent and human lung cells in tissue culture exposed to marihuana smoke *in vitro* also tended to show reduced chromosome complements, but not increased incidence of chromosome breaks or gaps (Leuchtenberger, this volume). Diverse studies with rodent cells also indicate little interference with chromosomal replication by cannabinoids (Bloch, this volume).

However, in contrast to purified cannabinoids, marihuana smoke has been reported to produce chromosomal aberrations and hypoploidy (Leuchtenberger, this volume), mutagenicity in bacteria as demonstrated by the Ames test (Busch *et al.*, 1979; Wehner *et al.*, 1980), and impaired development in the F_2 generation (the second generation of offspring) of treated animals (Fried and Charlebois, 1979). Studies to date have not shown cytogenetic abnormalities or mutagenic effects which are definitely attributable to cannabinoids, or unambiguously identifiable in the human population.

Carcinogenicity

Analysis of cannabis smoke, animal studies, and one clinical report suggest that cannabis may have significant carcinogenic potential. Cannabis smoke condensate ("tar") is a mutagen (see above) and when painted on animal skin has resulted in alterations of cell development (metaplasia) in the sebaceous glands (Magus and Harris, 1971) and tumor formation (Hoffmann *et al.*, 1975). Certain naphthalenes, particularly benzopyrene, are known to be as much as 70% more abundant in cannabis "tar" than in tobacco "tar" (Novotny *et al.*, 1976). Rodents made to inhale cannabis smoke for several months show changes in bronchial epithelium that are compatible with precancerous alteration (Rosenkrantz and Fleischman, 1979).

One study of bronchial biopsies in young men who were heavy users showed histopathological changes similar to those observed in much older smokers of tobacco cigarettes who may develop lung cancer (Tennant, 1980). The combination of tobacco plus hashish smoking may have enhanced the development of precancerous lesions.

One team of investigators has studied the effects of chronic exposure to fresh whole cannabis smoke and to its gas vapor phase on human lung tissue cultures (Leuchtenberger, this volume). Cellular abnormalities developed in essentially the same sequence which occurs with tobacco smoke, and appeared to be related to component(s) of the gas vapor phase of the fresh cannabis smoke. Abnormalities in mitosis, DNA complement and chromosomal number, as well as cellular proliferation, were observed. All these changes were more severe after exposure to cannabis smoke than to tobacco smoke. In hamster lung cultures, both cannabis and tobacco smoke led to malignant transformation; both types of smoke appeared to promote rather than to initiate malignant transformation. When the malignant cells were injected into athymic nude mice, fibrosarcomas developed. It has been reported that ascorbic acid protects human and hamster lung cell cultures from malignant transformation induced by cannabis smoke, but may enhance cancerous cell growth and dedifferentiation (conversion to more primitive cell forms) in human breast cancer cultures exposed to cannabis smoke. The significance of these findings is not yet clear.

At this time there is no confirmed evidence that cannabis has produced cancer in humans. Available information, however, indicates that cannabis has carcinogenic potential, and human users should be carefully surveyed and monitored for evidence of cancer development.

Impairment of Macromolecule Synthesis

Marihuana smoke (whole smoke) evoked a decrease in DNA content in spermatids (immature sperm) of cultured animal testis (Leuchtenberger, this volume). This alteration was not found in spermatids after exposure to the gas vapor phase of marihuana smoke, or after exposure to tobacco smoke (whole smoke or the gas vapor phase). Therefore the cannabinoids of marihuana smoke were probably mainly responsible for the alterations in DNA synthesis. Similar inhibition of DNA synthesis (decreased incorporation of ^{3}H-thymidine) has also been reported in cultured lymphocytes from human users of cannabis and from THC-treated monkeys, rats, guinea pigs, and mice, as well as in various unicellular organisms and cultured malignant cells exposed to THC *in vitro* (Munson and Fehr, this volume). Inhibition of RNA synthesis (decreased incorporation of ^{3}H-uridine) and of protein synthesis has also been reported in a similar range of preparations (Munson and Fehr, this volume).

In most of these studies, the concentration of THC added *in vitro* was 10^{-4}–10^{-6} mol/1 which is well above the range of THC concentrations found in the plasma or tissue fluids of human users of cannabis. But there is some difficulty in specifying concentration of THC since its maximum solubility in water is of the order of 10^{-6} mol/1 or less (Banerjee *et al.*, 1975), so that one must suppose the "free" concentration cannot rise much above this. In plasma, THC and its first metabolite, (11-OH-THC) are strongly bound (up to 99%) *in vivo* to lipoprotein or albumin. *In vitro*, the nominal concentration will be reduced by adsorption to glass and by uptake into the tissue or test material, and some of it may be bound either by protein in the culture medium, or by protein released by the tissue into the medium. The nominal concentration in such experiments must therefore be regarded as representing not "free" concentration, but the amount of THC available to be taken up by the test system. In the few studies in which tissue/medium ratios have been reported, the latter have been in the order of 100–600. The correlation of *in vitro* with *in vivo* work would be greatly aided by further study of these factors.

Possible Biochemical Mechanisms

Interference with macromolecule synthesis might result from various mechanisms; examples are failure of cellular uptake of the precursor substances, inhibition of the synthesizing enzymes, perturbation of the cellular membranes in which the enzymes are located, blockade of receptors for hormones which modulate the syntheses, and so forth. The evidence on these points is not reviewed here for reasons outlined in Section 1: Background and Objectives.

[Only one hypothesis is mentioned here in some detail, because it is recent and imaginative, and because it proposes a single explanation both for the deficiency in nuclear histone synthesis and for the ultrastructural alterations encountered in the leukocytes and spermatozoa of chronic human users of hashish (Issidorides, this volume). These cells are characterized by a depletion of the amino acid arginine and by abnormal chromatin condensation. According to this hypothesis, the biological effects observed in chronic cannabis users may be explained by arginine depletion which, in itself, can cause chromosomal aberrations, decreased sperm maturity and motility, defective ovulation, growth retardation, immunosuppression and the reactivation of latent viral infections, and CNS effects such as anorexia, motor incoordination, and lethargy. Furthermore, the enzymes reported to be affected by cannabis possess essential arginine residues at their active sites, which would permit a THC/arginine interaction.]

4. IMMUNE SYSTEM

The immune system in humans and other higher animals plays a major role in protecting the body against bacterial, viral, and other infections against the growth and spread of body cells which have undergone transformation to a cancerous state, and against foreign proteins and many other substances. A considerable number of scientific reports deal with the effects of cannabinoids on the various main components of the immune system in humans and experimental animals. These principal components are the T-lymphocytes, the B-lymphocytes (which form antibodies or immunoglobulins), and the macrophages.

Experimental Animals

In contrast to the conflicting findings so far available in humans, there is consistent evidence that THC and marihuana administered parenterally or by inhalation induce immunological defects in mice and rats, and that rats are more sensitive than mice (Munson and Fehr, this volume). The immunological responses that have been shown to be perturbed include:

1. humoral immune suppression in mice and rats, as measured by decreased antibody responses to T-dependent and T-independent antigens, and decreased lymphocyte response to a B-cell mitogen;
2. cell-mediated immune suppression in mice as measured by a reduction of the delayed hypersensitivity response to *Corynebacterium parvum*, sheep red blood cells, oxazolone and skin allografts, and decreased lymphocyte response to the T-cell mitogen, phytohemagglutinin (PHA). The depression of PHA-induced lymphocyte response was also seen in rats and monkeys.

These effects were obtained with doses of THC which produced very little behavioral effect in the mice. However, the molecular structural requirements for immunosuppressant action are different from those for psychoactivity (Smith *et al.*, 1978), so that cannabinoids other than THC many contribute to the suppressant effect of cannabis.

The evidence that marihuana or THC can perturb monocyte or macrophage function is mixed (Munson and Fehr, this volume). Overall there appears to be a reduction in the staphylococcus-killing ability of cells obtained by bronchopulmonary lavage from animals exposed to cannabis smoke, along with a reduction in the release of lysosomal enzymes, in superoxide formation and in oxygen consumption. Decreased phagocytic activity has also been observed after exposure of lung macrophages to cannabinoids or cannabis smoke *in vitro*.

The degree of immunosuppression produced by THC is a function of the temporal relationship between the administration of the cannabinoid and the antigen. The effects are more pronounced if the cannabinoids are administered during the early phase of antibody formation (Luthra *et al.*, 1980) and are more evident in young animals (Pruess and Lefkowitz, 1978). The degree of tolerance that can develop to these effects is not yet clear.]

The role of adrenal steroids in the immunosuppressive action of the cannabinoids is not clear. One study (Smith and Munson, 1976) suggests that a cannabinoid-induced increase in corticosteroid release may mediate certain aspects of the immune suppression (e.g., splenic atrophy), but not others (e.g., the inhibition of antibody formation).

Humans

[At present, there is only suggestive but not conclusive evidence that consumption of cannabis or THC may produce immune dysfunction in humans as measured by the following immunological indicators (Munson and Fehr, this volume):

1. the numbers of T-lymphocytes, B-lymphocytes or macrophages
2. the functioning of T-lymphocytes, B-lymphocytes or macrophages
3. serum immunoglobulin levels.]

The numerous studies in which these indicators have been used have yielded roughly similar numbers of reports of increased, decreased, or unaltered immune responses in cells from cannabis users compared to nonusers.

There is suggestive evidence that T-lymphocyte function may be impaired, as measured by a reduced responsiveness to mixed lymphocyte cultures or to PHA, and reduction in the number that can form rosettes with sheep red blood cells.

There is one report that the phagocytic ability of polymorphonuclear leukocytes is impaired in subjects smoking marihuana (Petersen *et al.*, 1975). There is also one report of biochemical and ultrastructural changes in the leukocytes of chronic hashish smokers (see Section 3: Possible Biochemical Mechanisms) (Stefanis and Issidorides, 1976; Issidorides, 1979).

Biological Significance

If the effects of cannabis on the immune system, as examined *in vitro*, are of biological importance, it should be possible to demonstrate that they reduce the resistance of the living organism to infection or to cancer although the latter effects might be altered by an inhibitory effect of THC on the cancer cells directly. Decreased resistance to infection by

Listeria monocytogenes and to herpes simplex virus has been found in cannabis-treated mice (Morahan *et al.*, 1979). Since other drugs which suppress immune responses in mice also do so in humans, the apparent differences between the findings with cannabis in humans and rodents may depend merely on relative doses used. In humans, it has been reported that dormant genital herpes infections have been reactivated shortly after the smoking of cannabis (Juel-Jensen, 1972).

It can be expected that the immunosuppressant efficacy of cannabis, like that of any other immunosuppressant drug, will vary along a continuum, ranging from little or no effect against immunity to common viral infections such as influenza, up to marked suppression of resistance to unusual infections such as Listeria pneumonia in the mouse. Since immunological function is normally less effective in older persons than in younger ones (Hallgren *et al.*, 1973; Burnet, 1976), it is also possible (though not yet studied) that the immunosuppressant effect of cannabis would be appreciably greater in the elderly. The magnitude of public health consequences of such a drug effect is therefore difficult to assess. One of the problems of interpretation of these findings is the relative crudeness and high variability of the tests of immune function *in vivo* compared to those *in vitro*. It is necessary to have a high degree of immunosuppression *in vitro* before a statistically significant *in vivo* effect can be demonstrated in a small number of experimental animals. Therefore some immunologists consider the *in vitro* effects of cannabis to be without functional significance for health.

However, epidemiological observations on large populations of users should permit a clearer assessment of the biological significance of small degrees of impairment of immune function. A minor degree of immunosuppression in a substantial number of cannabis users might result not in any sudden and dramatic increase in incidence of unusual infections, but rather in a slight increase in incidence, severity, and duration of common ones. Cumulatively, this could have considerable significance for public health and health care delivery systems.

Cannabis As an Allergen

Cannabinoids have some allergic potential. From the few data available, it appears that allergic reactions in humans are uncommon, although cannabis use has been reported to worsen allergic symptoms in atopic persons (Tennant *et al.*, 1971). Skin tests in cannabis smokers have usually shown little or no reaction to cannabis or its constituents (Tennant *et al.*, 1971; Lewis and Slavin, 1975), although some cannabis users have demonstrated serum antibody responses to THC and other cannabinoids, suggesting that these compounds can act as haptens (Liskow *et al.*, 1971; Shapiro *et al.*, 1976). Antibodies have also been made against THC in experimental animals (e.g., Lecorsier *et al.*, 1977).

5. EFFECTS ON ENDOCRINE FUNCTION

As with the work on the immune system, fairly impressive and consistent effects of cannabis have been observed in endocrine functions in experimental animals, while only weak and inconsistent effects have been reported in humans (Bloch, this volume). It is not clear whether this represents a species difference or a consequence of differences in dosage and pattern of administration, or of clinical variation. The endocrine responses of experimental animals to most other drugs are at least qualitatively similar to those of humans, although there are exceptions to this statement. Therefore, when a particular endpoint or system reacts uniformly to cannabinoid exposure in several species of several classes, including monkeys, a qualitatively similar response in humans may be anticipated.

Methodological Considerations

A number of the hormones studied, such as testosterone and luteinizing hormone (LH), show very large, short-lived, and quite irregular variations in blood levels, independent of any regular diurnal rhythms (De Lacerda *et al.*, 1973). Therefore occasional measurements at single points in time show very wide scatter and large standard deviations in small groups of normal subjects. In order to demonstrate reliable though small differences between groups submitted to different treatments, it is necessary to use either:

1. very large numbers of subjects, so that the standard error of the mean for the group is decreased in correspondence with the sample size, or
2. frequent or continuous sampling (e.g., by indwelling venous cannula), to estimate the true mean for each subject.

In human studies, (1) is probably not feasible for financial reasons, but (2) has been employed in the best recent investigations (e.g., Mendelson *et al.*, 1978).

In animal studies, published work has been deficient in a variety of important ways:

1. often only single doses of cannabinoids have been used, rather than full log-dose/response curves, so that the biological significance of the findings is difficult to determine;

2. *in vitro* drug concentrations may often be too high to be relevant to *in vivo* levels of cannabinoids (see Section 3: Impairment of Macromolecule Synthesis);
3. the duration of cannabis treatment is often variable and arbitrary;
4. the time between drug administration and hormone measurement is variable and often not stated;
5. animal strains are occasionally not specified;
6. data variance within the same study often differs widely;
7. in most experiments, cannabis-treated animals are compared with vehicle-treated controls, but for explanation of mechanisms there should also be comparisons with analogs, homologs, and derivatives of THC.

Despite these shortcomings, a good measure of agreement has been found in relation to the effects of cannabinoids on male and female gonadal and adrenal hormone production and on hypothalamic-pituitary regulation. Much less is known about the effects on other hormones.

Male Reproductive Hormones

Experimental Animals

In rats and mice, cannabinoids disrupt normal *male reproductive* physiology (Bloch, this volume). Testicular metabolic activity and *in vitro* testosterone synthesis are decreased; plasma levels of both testosterone and LH fall, and, upon chronic intake, androgenic target tissues show varying degrees of functional and morphological involution. Prolonged cannabinoid intake leads to diminished spermatogenesis. The effects of marihuana and cannabinoids on male reproductive endocrinology and on spermatogenesis are apparently reversible, since no permanent changes have been described following cessation of cannabinoid intake. These effects have been studied mainly in immature and pubertal rats. There is a need for corresponding studies in mature male rats.

Humans

Only a few studies have been carried out with modern methods of hormone measurement. These have involved young healthy users of cannabis, either with or without controlled experimental administration of cannabis as part of the study design. A few groups of investigators have reported reduced plasma levels of LH and/or testosterone and reduced sperm counts in the users, while other groups have found no changes

(Bloch, this volume). To date the difference has not been satisfactorily explained, but in view of the findings in the animal studies, it is possible that the cannabis doses in the humans have been just at or below the lower margin of the effective range.

Female Reproductive Hormones

Experimental Animals

As in the male, the acute or single administration of THC to *nonpregnant female rats* transiently inhibits functioning of the hypothalamic-pituitary-gonadal axis (Bloch, this volume). Plasma LH and prolactin levels are decreased; the pre-ovulatory LH surge is suppressed, and estrus is delayed. Chronic intake of THC or crude marihuana extract seems to impair reproductive function reversibly. The uteri and the vagina show signs of morphological and functional involution, and ovarian function may be affected. Estrous cycles are inconsistently interrupted or abolished.

The few studies on monkeys and other nonhuman primates tend to confirm a suppressive effect of cannabinoids on pituitary gonadotropin release, and the blocking of ovulation (Bloch, this volume). Too few studies evaluating other parameters have been carried out to permit even tentative inferences.

In experimental animals, THC exerts few effects unique to pregnancy (Bloch, this volume). High doses suppress or diminish the maternal weight gain normally occurring during pregnancy. THC also decreases prolactin levels, which may explain the reduced and inadequate lactation seen in the postpartum, cannabinoid-ingesting rat.

✓ *Humans*

There is one preliminary report of an increased proportion of menstrual cycles that were either anovulatory or marked by an inadequate luteal phase in marihuana-smoking women as compared with a group of nonusers (Bauman *et al.*, 1980). Otherwise, this subject has been virtually unexplored in human females.

Adrenal Cortex

Experimental Animals

Pure cannabinoids and crude marihuana extract stimulate adrenal cortical function in rats (Bloch, this volume). Acute administration results in increased plasma corticosterone concentrations; long-term and short-term exposure lead to adrenal weight increase and thymus weight decrease.

Humans

Several studies in humans, however, have failed to show changes in adrenocortical function as a result of cannabis use or experimental administration (Bloch, this volume). Only one group (Benowitz *et al.*, 1976) has reported a decreased plasma cortisol response to insulin-induced hypoglycemia in THC-treated males. Again, the difference between the results in humans and animals may reflect differences in relative doses of cannabinoids. In the animal studies, adrenal activation was observed only after rather large doses of THC, and not proportionately at all doses. Therefore, it may reflect a nonspecific stress response, above a certain threshold dose, as has been reported with alcohol (Stokes, 1971; Kakihana and Butte, 1979). In the human studies, the doses used may not have been high enough to produce this.

Other Hormones

Very little information exists on the effects of cannabis on other endocrine secretions. Several animal studies have shown reduction of circulating thyroxine or triiodothyronine levels after acute or chronic administration of THC, but this has not been confirmed in humans (Bloch, this volume). Plasma growth hormone levels have shown variable responses to THC, according to the age of the rat and route of administration (Bloch, this volume). There is one report of decreased growth hormone response to insulin injection in humans taking THC by mouth (Benowitz *et al.*, 1976).

Locus and Mechanisms of Action

Experimental animal studies have shown the primary locus of cannabinoid action to be in the brain, probably in the hypothalamus (Bloch, this volume). Cannabinoid stimulation of the adrenal cortex can be abolished by agents and procedures which block pituitary ACTH production, while LH-releasing hormone will stimulate pituitary LH release in the THC-blocked rat.

Crude marihuana extract and THC probably also exert a direct inhibitory effect on gonadal and adrenal cortical function. This is especially true for the testes, where *in vivo* and *in vitro* experiments have demonstrated an inhibition of testosterone synthesis, perhaps via reduced cholesterol esterase activity. Another possible mechanism is inhibition of testicular synthesis of prostaglandin E which is involved in mediating trophic hormone effects. Diminished metabolic activity and decreased macromolecule synthesis in testes following exposure to cannabinoids may explain the reduced spermatogenesis observed after cannabis intake.

Repeated administration of cannabinoids may result in a direct effect on the uterus, and possibly also on prostate and mammary gland tissue (Bloch, this volume). Interpretation of the data is made difficult by the fact that some investigators have used cannabis extracts while others have used THC. These preparations differ in their respective dose-response relations for each effect. If direct effects exist, they occur at larger doses than are needed to produce indirect effects (e.g., via actions on the hypothalamus and the pituitary), and may reflect a more general toxicity.

The molecular mechanism of cannabinoid action remains to be elucidated. It must also be remembered that marihuana contains other components which may have activity with quite different loci of action.

6. REPRODUCTION AND DEVELOPMENT

The effects of cannabinoids have been investigated to a very limited extent on aspects of reproduction and development other than the endocrine aspects mentioned in Section 5.

Sexual Behavior

Although there are descriptive references to decreased potency, sexual activity, and fertility of males in India, North Africa, and other regions of the world (e.g., Chopra and Chopra, 1939; Bouquet, 1951), attributed to heavy use of cannabis, these observations are not accompanied by any investigation adequate to support a causal link. In more recent field studies, both the users and their spouses indicated that sexual behavior was normal, but the users stated that they often smoked cannabis in order to prolong or be able to enjoy coitus (Page and Carter, 1980). A few experimental studies have reported decreased sexual reflexes and increased latency to mount in male rats (e.g., Corcoran *et al.*, 1974).

Clearly, the effects of cannabis on sexual behavior require considerably more systematic research.

Fertility

In animals, fertility in males and females has not been significantly altered by subchronic or chronic treatment with THC or cannabis extracts (Grilly *et al.*, 1974; Wright *et al.*, 1976).

In one study in humans, it was claimed that sterility was twice as common among chronic cannabis users as among the general population (Chopra and Chopra, 1939). However, there is no consistent evidence of decreased fertility, as indicated by the number of offspring of males who are chronic cannabis users (True *et al.*, 1980). Fertility has hardly been studied in female users of cannabis. If, as preliminary studies suggest, ovulation is suppressed by THC treatment, fertility would be adversely affected.

Teratogenesis

Any drug could potentially affect fetal development in two ways. First, exposure to a mutagenic agent prior to conception could alter the germ cells of the male or the female and thus influence the expression of the genes in the offspring. Cytogenetic effects of cannabis have been reviewed in Section 3: Chromosomal Aberrations and Mutagenicity. As noted there, it seems doubtful that crude cannabis extracts or THC are mutagenic in humans, although pyrolysis products present in cannabis smoke may have mutagenic activity.

Secondly, if exposure occurs during pregnancy, drugs can produce direct toxic effects on the fetus. THC administered to pregnant rodents results in a concentration gradient of mother > placenta > fetus (Bloch, this volume). The placenta takes up THC more avidly than the fetal tissues do, but releases it only slowly. This makes the placenta potentially a barrier against, but also a reservoir for, THC transfer into the fetus. A THC-induced disruption of placental development or function as suggested by preliminary observations of Sassenrath *et al.* (1979) may be significant, and could contribute to abnormalities in the fetus.

Cannabinoid administration during the first two-thirds of gestation is associated with increased frequency of fetal resorption and decreased birth weights in mice, rats, rabbits, and hamsters (Bloch, this volume).

There are three reports that the administration of large doses of THC to mice during the critical periods of palate and brain development correlates with increased frequency of cleft palate and exencephaly respectively (Mantilla-Plata *et al.*, 1975; Joneja, 1976; Bloch *et al.*, 1979). Cannabinoid-exposed hamsters also had an increased incidence of malformations (Geber and Schramm, 1969). Other reports of cannabinoid-induced malformations cannot be considered as definitive, and the majority of studies in these species have demonstrated no significant teratogenicity. Cannabis extracts may contain constituents other than THC which are teratogenic. The few reports of teratogenicity in rodents and rabbits (Bloch, this volume) indicate cannabinoids to be, at most, weakly teratogenic in these species, and the activity, if any, may reside in cannabinoids other than THC, or in noncannabinoid constituents of cannabis or cannabis smoke.

The teratogenic potential, however, has never been accurately assessed in humans. A major prospective study (Zukerman *et al.*, 1981) now in progress, should provide valuable information in this area.

Postnatal Development

Drug effects on postnatal development may be exerted through alterations in ability of the lactating mother to feed the young adequately, through alterations in other maternal behavior towards the young both during lactation and after weaning, and through tissue alterations in the offspring themselves as a result of drug exposure *in utero* and/or via the milk. In animals, and presumably in humans, cannabinoids can cross the placenta, and are also secreted in the milk (Chao *et al.*, 1976).

There has been very little systematic study of cannabis effects on general maternal behavior toward the offspring. However, animal studies have shown repeatedly that cannabis can impair lactation, probably by central actions leading to reduced prolactin output. This results in neonatal malnourishment, unless cross-fostering procedures (i.e., allowing untreated mothers to rear drug-exposed offspring) are used; consequently there is retardation of weight gain and skeletal growth, and increased neonatal mortality. A clear-cut maldevelopment of any other type such as delayed eye opening or incisor eruption is less often reported (Bloch, this volume). Follow-up observations, now in progress, of babies born to mothers who have smoked cannabis during pregnancy will be informative in this regard (Fried, 1980).

A major concern is the possibility of retardation of later juvenile maturation and development as a result of either *in utero* exposure or early commencement of cannabis use by children and adolescents. This has been until now an almost totally neglected research field and requires specific attention.

7. EFFECTS ON NERVOUS SYSTEM FUNCTION

Effects of Cannabis on Behavior

Acute Effects on Intellectual Functions

The effects of any drug on behavior are markedly influenced by a wide variety of factors, both within the individual user and derived from the environment at the time of testing. This is just as true of cannabis as of any other psychoactive drug. Consequently the picture of effects seen in any given instance depends on the relative contributions of the drug-specific effects (which are relatively predictable and reproducible) and of the individual and environmental influences (which are much more variable and less predictable). As a result, the behavioral effects of low doses of cannabis are relatively nonspecific and can show extensive overlap with those of amphetamines, opiates, hypnosedatives, and alcohol. In contrast, at high doses the cannabis effects are much more characteristic and identifiable. This is true not only for behavioral effects, but also for neurotoxicity and psychiatric effects, which are discussed in the following sections of this report.

In studies with rodents, dogs, and monkeys, behavioral profiles reveal a biphasic dose-effect and time-effect relation of cannabis and of THC. At low doses, hyperactivity and hypersensitivity (particularly to auditory and tactile stimuli) are evident, and there is synergism (mutual enhancement) with the corresponding effects of amphetamines and of low doses of opiates. At higher doses, ataxia, hypomotility, stupor, or coma are encountered, and the corresponding effects of other central depressant drugs are enhanced (Rosenkrantz, this volume). Biphasic patterns of changes in spontaneous activity related to both time and dose have also been described repeatedly in humans (Jones, 1980).

These changes do not, in themselves, constitute adverse effects; rather, they are the characteristic features of intoxication with cannabis. They are adverse effects only when they compromise the health or safety of the user or of others, by impairing the user's ability to carry out necessary cognitive-perceptual or psychomotor functions. The main conclusions concerning the effects of cannabis on these functions can be summarized as follows (Klonoff, this volume):

1. A host of studies have demonstrated impaired functioning on a variety of cognitive and performance tasks during marihuana intoxication;
2. impaired memory, altered time sense, and decrements in performance on a number of tasks—such as those involving reaction time, concept formation, learning, perception, motor coordination, attention and signal detection—are commonly described in the literature;
3. in most laboratory studies, the duration of measurable memory alterations is a few hours after a smoked marihuana cigarette. However, for some marihuana smokers, there may be more lasting problems with transfer of new information into long-term memory storage;
4. greater appreciation has developed for the need to study a range of

doses on a variety of cognitive tasks before trying to describe the effects of marihuana. For the most part, impairments are dose-related but there are apt to be multiple marihuana effects depending on the exact demands of the task; for example, performance on some cognitive tasks might even improve when low doses are used;

5. motivation to perform well can be enhanced by incentives (e.g., more money for correct responses) and this enhancement can decrease some marihuana effects.

Acute Effects on Driving Skills and Driving Performance

Retrospective sources of information concerning the effects of cannabis on driving include:

1. self-reported experiences and perceptions of users
2. anecdotal reports by investigators
3. data collected after accidents or traffic violations.

On the basis of such accounts, there appears to be a consensus that marihuana can, and often does, impair driving ability and actual driving performance (Klonoff, this volume). There has been growing evidence that marihuana, used alone or in combination with alcohol and other drugs, is implicated in traffic accidents and fatalities (Sterling-Smith, 1974; Woodhouse, 1974; Cimbura *et al.*, 1980). The nature of this implication, however, is less than clear. Toxicological data, including measurement of cannabinoid metabolites in the urine, may mean only that the person has used cannabis at some relatively recent time (hours to days) before the time of sampling (Rubenstein, 1979). Such information obviously provides no causal link between the drug use and occurrence of an accident. Much greater attention must therefore be given to prospective studies of cannabis effects.

Prospective methods of investigation include:

1. psychomotor tasks that are presumed or known to be related to driving skills
2. driving simulators
3. traffic-free driving test courses
4. road tests under actual traffic conditions.

Psychomotor tasks can test only specific subsets of the complex behavioral demands for driving. While many such studies have reported dose-related impairment of driving skills by cannabis, there is a real question about generalizability to actual driving situations.

Driving simulators have the advantage of permitting control of many variables, but are nevertheless subject to experimental artifacts. The studies to date have operationally defined variables such as speed errors, accelerator errors, brake errors, risk-taking in terms of passing, passing-time judgments, and visual signal detection (Klonoff, this volume). Dose-related effects of cannabis on most of the measures employed have been reported, but again there is a question about generalizing to real-life driving since most of the emotional and motivational factors in real-life driving performance are missing from the simulator tests. Three published studies (Le Dain, 1972; Smiley *et al.*, 1974; Hansteen *et al.*, 1976) have reported cannabis dose-related impairment of driving performance. Skilled drivers, on traffic-free test courses, have repeated errors similar to those observed in driving simulator studies.

The most sophisticated study (Klonoff, 1974), and probably the most relevant, is an investigation of actual driving in downtown rush-hour traffic, in cars with dual controls to permit the observer to make the corrections required for safety. Experienced drivers were tested under placebo, small and moderate doses of marihuana, in a double-blind crossover design. Composite driving performance was improved in some cases, unchanged in others, and worse in the majority, compared to the predose control period. However, the number of those who improved or remained unchanged under marihuana was smaller than under placebo, while the number who deteriorated under marihuana was larger than under placebo, and the shift was significantly greater with the higher dose of marihuana.

These findings provide a striking demonstration of the ability of even small doses of marihuana to impair driving ability. Whether or not this is translatable into the production of automobile or airplane accidents will obviously depend upon the degree of impairment relative to the margin of safety between the situational demands and the operator's remaining skills under the drug. There is a need for independent replication of this work, preferably with inclusion of higher test doses, and combinations of cannabis with alcohol and other drugs. Night driving studies should be included, if possible. It is also not known to what extent the degree of impairment observed in these studies might be modified by cannabis tolerance, and by the age and experience of the driver.

Chronic Effects on Behavior

Experimental animals. Animal studies have indicated that chronic exposure to cannabis can modify the acute behavioral effects not only by the development of tolerance (see Section 9: Tolerance and Physical Dependence: Their Relationship to Drug-Seeking Behavior) (Jones, this volume), but also by the sudden appearance of new manifestations of behavioral change after several months of administration (Rosenkrantz, 1982). Prominent among these in rats and monkeys are irritability on handling, and increased aggressiveness between animals of the same or other species. Not all investigators have observed these changes, and in some species (e.g., dog) weakness and lethargy have predominated. Therefore it might be questioned whether the aggressiveness is a specific effect of cannabis inhalation or a nonspecific result of repeated exposure to noxious stimuli. The relative lack of aggressiveness in control rats exposed to the noxious stimulus of smoke from cannabinoid-free marihuana tends to support the view that there is a specific drug effect (Luthra *et al.*, 1976).

Humans. In humans, a number of studies have indicated cannabis-induced impairment of short-term memory by interference with the acquisition and storage phases rather than with initiation and recall (Ferraro, 1980; Klonoff, this volume; Mendelson, this volume). This appears to involve lack of concentration on the task, and may be modified by specific motivational factors. These effects on memory appear to persist undiminished through a three-week period of daily smoking of marihuana under experimental closed-ward conditions (Rossi *et al.*, 1977). Speech and interpersonal behavior have shown only slight and subtle changes under marihuana (Mendelson, this volume), but the observations have been made only during single sessions or relatively short-term repeated observations. The field studies of long-term heavy users so far conducted have shown no major changes in social behavior (Rubin and Comitas, 1975; Fink, 1977; True *et al.*, 1980), but there are deficiencies of design in these studies, as described in Section 9: Selection of Subjects and Designs for Clinical Experiments.

Neurotoxicity

It is difficult to avoid arbitrariness in distinctions between behavioral effects of a drug, and drug-induced neurotoxicity. For the purposes of this report, "neurotoxicity" is used to refer to functional aberrations that appear to be qualitatively distinct from those which are characteristic of the usual pattern of reversible acute and chronic effects, and that might be caused by identified or identifiable neuronal damage.

Experimental Animals

Chronic exposure. In animal studies, two alterations of behavior have been noted to appear during the course of prolonged periods of cannabis treatment (Rosenkrantz, this volume). Sixty percent of rats exposed repeatedly to cannabis smoke for five weeks or longer develop a pattern of sudden vertical jumping which has been labeled the "popcorn reaction" (Luthra *et al.*, 1976). This is also seen in young animals exposed chronically to cannabis *in utero*, and then challenged with a single small dose of THC at 30 days of age (Rosenkrantz, 1979). Electrical and motor seizure activity have also been noted in several studies (Rosenkrantz, this volume), but the definition of abnormal spike-like wave forms reported in the EEG of the cannabis-treated animals has not been made according to rigorous criteria, and the frequency has not been assessed quantitatively. Nevertheless, the claims of neurotoxicity during chronic cannabis exposure raise the possibility that long-lasting residual changes might be found.

Residual changes. Animal studies have shown no effect of chronic cannabis administration on brain weight or histology as evident under the light microscope (Fehr and Kalant, this volume). There has been one claim (Heath *et al.*, 1980) of residual alteration of synapses in the septum, hippocampus, and amygdala, as revealed by electron microscopy, but technical objections have been raised to this work (Institute of Medicine, 1982) and the reported alterations are not easily quantifiable in statistical terms. EEG observations in animal studies have shown the possible occurrence of withdrawal effects (Fehr and Kalant, this volume), and three reports suggest the occurrence of long-term residual abnormalities in EEG tracings from the cortex and hippocampus of cats (Barratt and Adams, 1972), rats (Fehr *et al.*, 1976, 1979), and monkeys (Heath, 1976) exposed to long-term treatment. However, these also lack critical quantitative analysis. There is only one group reporting diverse residual neurochemical changes after long-term cannabis treatment (Luthra *et al.*, 1975a and b, 1976) and the functional significance of the findings is not at all clear.

Most studies of postdrug behavioral changes in chronically treated rats have been carried out too soon after the last drug administration to prove whether any residual effects are long-term ones or merely the slow disappearance of intoxication. However, two laboratories have reported decreased learning ability months after the end of long-term treatment (Fehr *et al.*, 1976, 1979; Radouco-Thomas *et al.*, 1976; Stiglick and Kalant, 1982a and b). The alterations found raise the possibility of changes in the hippocampus, since the tests used include conventional and radial maze learning, operant behavior involving time discriminations (DRL schedules, i.e., differential reinforcement of low rates of responding), open-field exploration, and two-way shuttle box avoidance learning; correct performance of these tests is dependent on spatial orientation or on response inhibition, both of which are believed to depend heavily on intact hippocampal functions.

Prenatal exposure. Several studies of prenatal exposure have indicated that the offspring of cannabis-treated animals show small delays in various stages of postnatal development, such as eye-opening, reflexes of several types, and open-field exploration (Fehr and Kalant, this volume). However, the development appears to be back to normal by several weeks or months after birth. This could mean either that no residual damage was present, that remaining damage was too slight to be detected by available measures, or that plasticity of nervous system organization in the newborn permitted adequate compensation for the loss of function of any damaged cells. Charlebois and Fried (1980) reported that the retarded development did not occur in groups of cannabis-exposed rats that were fed an enriched protein diet during pregnancy. This suggests that prenatal nutrition (possibly mediated by cannabis-induced anorexia) is a factor in the development of postnatal deficits.

Humans

Amotivational syndrome. Numerous clinical reports from several countries have described heavy, chronic cannabis users who exhibit behaviors that some observers have labeled "amotivational syndrome" (Fehr and Kalant, this volume). Included in the various descriptions of this syndrome are the following characteristics: apathy; reduced drive and ambition; impaired ability to carry out complex tasks; failure to pursue long-term plans; reduced tolerance to frustration; diminished communication skills; neglect of personal appearance; and sluggish mental responses. The syndrome takes several weeks to clear after the termination of drug administration. This fact suggests that the symptoms are related to CNS changes rather than to the continued presence of THC. Since no estimations of plasma or tissue THC levels in chronic users are available, the actual mechanism cannot be resolved. A variety of clinical studies and reports in the past decade clearly reveal, however, that the "amotivational syndrome" is neither diagnostic of, nor specific to, chronic cannabis use. The signs and symptoms of the "amotivational syndrome" are essentially those found with chronic intoxication with a number of psychoactive drugs, particularly those that are sedative-hypnotic in nature. It may, therefore, be more appropriate to refer to "chronic cannabis intoxication" and discard the nonspecific term "amotivational syndrome."

At this time the dosage of cannabis or the frequency and duration of cannabis exposure required to produce chronic intoxication are not precisely known. Well controlled clinical studies and close clinical observations (Mendelson, this volume), however, indicate that this picture is not particularly common. In addition, personality and concomitant drug-use factors make it difficult to diagnose this state, or to specify that cannabis, *per se,* may produce alterations in motivation.

Residual brain damage. Human studies after the end of a period of chronic intoxication with cannabis have generally yielded no evidence of residual brain damage. There has been one report of cerebral atrophy, as indicated by air encephalography, in young cannabis users complaining of a variety of neurological symptoms, including memory and cognitive dysfunction (Campbell *et al.*, 1971). However, no atrophy was found in later studies in which computer-assisted tomographic (CAT) scans were performed in young cannabis users who were not also regular users of other drugs, and who were totally asymptomatic (Co *et al.*, 1977; Kuehnle *et al.*, 1977). CAT scans also failed to demonstrate cortical atrophy in monkeys treated chronically with cannabis extract by mouth (Rumbaugh *et al.*, 1980).

Most studies which have compared the performances of chronic users and controls in neuropsychological tests have failed to elicit significant differences. Significant cognitive deficit is not a commonly demonstrated effect of chronic use of cannabis in clinically healthy subjects. However, to provide an appropriate comparison, most daily users of alcohol are healthy and do not show cognitive deficits, even though such abnormalities are common in clinically diagnosed alcoholics (Parsons and Farr, 1981; Wilkinson and Carlen, 1981). Therefore, it is clear that studies on relatively small samples, such as are at the moment available for cannabis, cannot be expected to rule them out.

The overall conclusions from a review of this literature are hampered by a general inadequacy of reported data, especially in the clinical studies, which have often been characterized in the past by poor sample size and selection; poor or no differentiation between intoxication, withdrawal, and residual change; and an absence of before-and-after longitudinal studies of regular users. The animal studies which revealed long-lasting impairment of learning ability after a period of chronic cannabis treatment raise the clear possibility that residual long-lasting damage can be caused by cannabis, but a decision as to whether or not it does occur in humans will probably have to await the performance of adequate confirmatory studies on brains from long-term users.

Prenatal exposure. In a follow-up study of a small number of babies exposed daily or less frequently to marihuana *in utero*, Fried (1980) observed dose-related abnormalities in responses to visual stimuli and an increased prevalence of irritability, tremor, and startle responses as compared to a group of nonexposed controls. Since the babies were observed only at two or three days postpartum, the described symptoms may have been the manifestation of a neonatal abstinence syndrome of the type described for a variety of CNS depressant drugs (Finnegan and Fehr, 1980). Ongoing assessments of these, and additional children, should yield information on the persistence and significance of these symptoms.

Psychiatric Effects of Cannabis Use

Acute Consequences

✓ Acute panic and ✓ paranoid states are the most commonly observed short-term adverse psychological effects of cannabis use (Negrete, this volume). The validity of these conditions is no longer questioned, as they have been seen both in clinical settings and in laboratory experiments. The marked difference in frequency with which such problems are reported in different countries, and the diminishing frequency of clinical reports on this type of reaction in Europe and North America, tend to support early contentions that they may be due mainly to adverse social conditions and the user's lack of experience. Alternatively, the decreased frequency of such reports might be due to loss of novelty, and therefore decreased incentive for physicians to describe additional cases in the clinical literature. Nevertheless, it has now been satisfactorily demonstrated that setting alone does not explain their occurrence. Additional work is needed to identify the intervening pharmacological, neurophysiological, and psychopathological factors.

Other acute reactions of increasing clinical relevance are ✓ severe dysphoric states which have been observed in the course of THC therapy (e.g., Shiling *et al.*, 1980). Such reactions were described frequently in the clinical literature at the turn of the century when therapeutic use of cannabis extract was common. A concerted effort must be made to develop specific treatment procedures with a view to preventing or minimizing these untoward psychiatric side-effects, especially in older subjects.

Problems Related to Chronic Use

These are seen mainly in younger users, principally males. This may be more a reflection of the criteria for defining "problems" or "cases" than of real differences in frequency of occurrence in different groups of users. The problem of "amotivational syndrome" has been covered in Section 7. The most important other chronic psychiatric complication is that of cannabis-related psychosis.

[The only cannabis-induced psychosis picture which is supported by sufficient evidence to this moment is a short-lasting condition—from a few days to four weeks—with symptoms of mental confusion, memory impairment, regressive and impulsive behavior, delusional formations, and sensory-perceptive distortions (Negrete, this volume). The frequency of occurrence in Western societies is quite low, and it seems to affect mainly very heavy users. A commonly found predisposing factor is a high degree of premorbid personality disturbance. This condition can be expected to show a rising incidence as the numbers of daily and heavier users in the population increase. More research is needed to identify risk factors other than excessive use.

A highly relevant area of research where current data are clearly too limited, is the problem of cannabis influence on independently occurring psychiatric illness. The evidence already available, however, is sufficient to warrant large-scale prospective studies on the effects of cannabis on the phenomenology of some of the most prevalent psychiatric disorders, in terms of both symptomatology and evolution (Negrete, this volume). Also, specific research is urgently needed on the interaction between cannabis and chemical agents commonly used in psychiatric pharmacotherapy, including its possible influence on therapeutic response.

Flashback

Most of the evidence available on the recurrence of drug-related symptoms during abstinence (flashbacks) originates from self-report answers to rather imprecise questionnaire surveys, and from subjective descriptions given by individuals who believe they have experienced flashbacks (Negrete, this volume). The systematic phenomenological analysis of this clinical condition has been largely neglected, and controlled studies of the intervening etiopathogenic factors do not appear to have been carried out up to the present.

Cultural Influences on Cannabis Use and Its Consequences

Social role of cannabis and social control of its use. The most prevalent purpose of cannabis use in most cultures appears to be the recreational one, both in societies where it has been practised in a traditional manner and in those which have only recently adopted it. Medicinal and ceremonial/ritual patterns of use have also been observed, but clearly more in nonindustrial than in industrialized societies (Mohan, this volume).

There appear to be major cross-cultural differences in the type of population involved in cannabis use at this time. Poorer, older, and more predominantly male sectors are typical in nonindustrialized societies (Mohan, this volume). In industrial countries, sex differences are relatively minor and the use tends to be confined to adolescents and young adults (Smart, this volume).

However, as is the case with other drugs of abuse, there seems to be an incipient trend towards universalization and homogenization of cannabis use patterns. Patterns in other countries are tending toward the North American picture, particularly in larger urban populations around the world (Mohan, this volume).

There are cross-cultural differences in setting of use, type of cannabis preparations preferred, route of intake, dose levels, and the concomitant use of other psychoactive agents. Oral ingestion, for instance, is more prevalent in societies in which cannabis use is traditional. Such societies appear to attribute great importance to the variations in the psychoactive potency of the different cannabis preparations in use. Social reaction towards use may vary in accordance with the type of product involved. In India, for example, there is considerably more social lenience towards the use of cannabis leaf material than to that of resin. In the past, social control mechanisms have varied cross-culturally in accordance with local social perception of use. To the extent that legal controls come to be determined by national and international perceptions and agreements, such variations tend to disappear. It is conceivable that the repeated use of cannabis would be perceived as a greater threat in the more industrialized societies, where individuals are under higher pressure in regard to productivity and mental performance.

These differences in patterns of use and level of social acceptance probably influence the levels of use and the expectations of drug effect. Therefore they may also be expected to affect the types and incidence of various behavioral and health consequences of cannabis use.

Behavioral effects. The available literature includes reports of cultural variations in the behavior of individuals under the effects of cannabis (Rubin, 1975). Attitudes varying from aggression, psychomotor agitation, and delinquent tendencies, to passivity and easier conviviality have been recorded as typical of cannabis effects in different parts of the world. Most such differences are likely to be determined by factors other than the pharmacological action of the drug and should be scientifically re-examined. Another item that requires exploration is the possibility of ethnic variation in drug response, which has not yet been studied systematically with respect to cannabis.

Psychiatric consequences. It is quite possible that there is less cross-cultural variation in the psychiatric consequences of cannabis use than was previously believed. The higher frequency of "cannabis psychosis" observed in North Africa and India, for example, may soon disappear as the validity of this diagnosis is being questioned and the use of this term is being abandoned in those regions. However, the difference in prevalence of dose-related acute reactions is likely to remain as long as there are major cross-cultural differences in the potency of cannabis preparations used.

Neuropsychological testing. At present, there is no satisfactory evidence that culture in itself may explain variations in neuropsychological test performance, provided that the tests have been properly validated in each population where they have been used.

8. EPIDEMIOLOGY

Sources of Information

A large number of studies mainly in developed countries have produced a variety of data about cannabis use. Among the most common epidemiological sources are those listed below:

Self-report surveys of users

Observations of users

Official registration and notification records

Studies of special populations of high-risk groups

Hospital, clinic, and emergency service admissions

Arrest and conviction records

Social and welfare agency records

Production and seizure records.

All of these sources are potentially able to give relevant and good information, although each has certain clear limitations with respect to the specific groups studied, which do not always allow generalized interpretations.

Various methodological defects impair the accuracy and uniformity of data collection, especially from self-report studies and from routine statistics of health care delivery systems. Clinical patients represent a self-selected population. Where cannabis use is illegal, it may not be reported by the user with a health problem for fear of self-incrimination, unless confidentiality of medical records is guaranteed. In emergency treatment services, the need for prompt treatment often interferes with thorough collection and recording of information on drug use, especially when the ratio of treatment staff to case load is low. High turnover of staff may create major difficulties for systematic data collection, unless there is continuous training of new personnel and use of specific incentives for accurate recording of histories. Nevertheless, information from such sources may give useful indices of the relative magnitudes of problems related to different drugs. More detailed discussion of these questions, and specific recommendations for steps to solve them, are contained in a recent report of the WHO Expert Committee on Implementation of the Convention on Psychotropic Substances, 1971 (1981).

Despite the shortcomings in the accuracy and uniformity of data collection, and the low quantity and quality of data in some countries, much is known about incidence and prevalence of cannabis use (Smart, this volume). However, there is less epidemiological knowledge about the adverse health consequences of cannabis use. This is not surprising, since the effects described in Sections 2 to 7 of this report are not specific to cannabis in the sense that Laennec's cirrhosis is fairly specific to alcohol (Schmidt, 1977). Therefore the diagnostic entities themselves cannot be used retrospectively as indicators of hazardous levels of cannabis use in a large population.

For this reason, assessment of the contribution of cannabis to the production of public health problems will require (a) long-term prospective studies of sufficiently large groups of users and nonusers to measure the comparative incidence and prevalence of various adverse effects, and (b) large-scale retrospective correlational studies, similar to those on tobacco cigarette use, when details of cannabis use have been recorded accurately in hospital case records for long enough to provide a suitable body of statistical data. Until such studies are carried out, we can have only rough impressions, at best, concerning the real magnitude of cannabis-related health problems.

The value of individual case reports (which are sometimes dismissed as "anecdotal" evidence) should not be overlooked. With cannabis as with any other drug, relatively uncommon but potentially serious untoward effects are usually identified first by astute clinicians and published as case reports. When attention has thus been drawn to a possible problem, it may then be possible to devise experimental studies of causal mechanisms, and large-scale statistical analyses.

Epidemiological Findings

Studies on Distribution of Cannabis Use

In general, recent epidemiological studies in developed countries (Smart, this volume) indicate that:

1. [In most countries that have been surveyed, cannabis has been used by about 17%–19% of the general population. Among the student populations, rates of "ever used" vary from less than 1% (Belgium) to more than 60% (U.S.A.), with most countries falling in the

range of 23%–32%. In both student and general populations, the proportion of daily users ranges from less than 1% to more than 11%, with the student groups tending toward the upper end of the range. The apparent average for the countries surveyed was 3%–4%.]

2. [In most countries with good trend studies (Canada, U.S.A., Australia) cannabis use has increased greatly since the late 1960s, i.e., the proportion of users has increased by a factor of 3 to 5. There are some recent signs of stabilization in use over the past few years in Mexico, the U.S.A., and Norway.]

In developing countries (Mohan, this volume) the picture is much less clear. Use of cannabis is widespread in Africa, the Middle East, southern and southeastern Asia, Hong Kong, and the Philippines, both among lower socioeconomic groups (agricultural and urban laborers, taxi and lorry drivers) and in affluent upper-class groups (adults as well as students). However, there is a scarcity of sound epidemiological studies of general populations, hospital/clinic patients, and selected population groups.

The main reasons for the scarcity of studies appear to be lack of finances and trained people to carry out the surveys, and the relatively low priority allotted to cannabis in the health sector, both nationally and internationally. Nationally, more urgent health problems, such as communicable diseases, nutrition, and sanitation, make stronger demands on scarce resources. Internationally, the Geneva Single Convention laid greatest emphasis on control and movement of opiates across national boundaries rather than of drugs such as cannabis.

One important aspect of use in some developing countries is the difference between socially sanctioned limited use of cannabis for ceremonial purposes, and socially unsanctioned regular use. In India, for example, the great majority of the Hindu population participates in ceremonial use, as in the festival of Shiva (Hasan, 1975), but regular self-administration is carried out by only a small fraction of the population (Mohan, this volume). If the unimodal distribution-of-consumption curve holds for cannabis in the same way as for alcohol, India would be expected to have a very low modal *per capita* mean daily consumption and a very low percentage of users employing large amounts, despite the availability of potent preparations. In contrast, in North America and Europe the absence of a prescribed social role for cannabis, and of traditional social controls of use, might pose a much greater risk of hazardous consumption as potent preparations become more widely accessible.

Epidemiology of Adverse Effects of Cannabis

Knowledge about the frequency of various adverse reactions to cannabis is difficult to assemble. The epidemiologist would like to know how often adverse reactions occur, in what types of users, and to identify the explanatory variables such as cannabis dose, previous drug use, and psychosocial characteristics (Smart, this volume). The epidemiologist would also like to know if there is a "safe" (nonharmful) dose of cannabis, and whether some users are *not* at risk for adverse consequences. Answers (such as they are) to these questions typically come from studies not ideally designed to answer them. Nevertheless we might be able to accept the following tentative conclusions about adverse reactions (Smart, this volume):

1. No studies of general populations have determined the rate of adverse reactions serious enough to require treatment or hospitalization. So far, no studies have been made of adverse reactions, whether of a serious or nonserious nature, in general *adult* populations of cannabis users.
2. Usually, studies of cannabis effects on biochemical and neurological functions give very little information on the frequency of adverse reactions to be expected in large populations of users (and, of course, were not designed specifically to do so). Typically, such studies use a selected and narrow range of the cannabis-using population as subjects, mainly young males experienced with cannabis. The sample sizes are usually small (less than 100), and hence the chances to detect uncommon forms of adverse consequences could be quite small.
3. The total number of patients with psychological adverse reactions reported from treatment facilities is not great for a drug used as extensively as cannabis. Unfortunately, this information does not permit calculation of a rate of incidence of such reactions. However, the low number reported suggests either that *serious* psychological disturbances from cannabis use are not common among users in general, without telling us just how uncommon, or that a large proportion of such cases is not reported in the literature.
4. Most of the reported adverse cases come from the U.S.A.; cases from outside the U.S.A. represent only about 42% of the total. That cases from the U.S.A. are over-represented should be expected, because rates of cannabis use and heavy use are higher there than in other Western countries.
5. More cannabis-related psychological problems have been reported for males than females, and for persons under than over 21. The ratio is about 3 males for 1 female, even when the survey studies with all-male military samples are deleted. The ratio of overall and daily use for males and females in the U.S.A., at least among young persons (from which most clinical cases of adverse reactions

come), is about 1.5:1. There is a clear suggestion that female users and older persons are at lower risk than young male users for serious psychological consequences of cannabis use, presumably because they consume smaller amounts and less frequently.

6. In about 80% of adverse reactions described in clinical studies, the patients reported the use of other hallucinogenic drugs as well as cannabis. The concomitant use of hallucinogens among these patients would be higher than among cannabis users in general but probably not much higher than among heavy users who have not sought treatment. However, surveys of users uniformly indicate that adverse reactions are more common among those who have used other hallucinogenic drugs.

7. There is the suggestion of a "safe" dose in the study of Tennant and Groesbeck (1972). These authors reported that users taking less than 10–12 g hashish per month had no adverse effects other than minor respiratory problems. A few instances of acute psychological adverse effects have been reported among experimental and infrequent users, thereby suggesting that there is no totally safe dose of cannabis. However, more than 80% of reported cases involve daily users.

8. Information on other demographic or personality variables is not included often enough to permit any conclusion about how they related to adverse reactions. An impression is gained that more than the expected numbers had previous psychological disturbances, but the methods of assessing them vary greatly. The expected rate of such disturbances in the population from which the reported cases are drawn is often uncertain.

In developing countries, there have been very few epidemiological studies of the adverse effects of long-term cannabis use (Mohan, this volume). Most studies are of the case-report type. This is unfortunate, since countries with traditional cannabis use are natural field laboratories. Only in India and Egypt have epidemiological studies of this aspect been attempted, and the results are equivocal. One Indian study (Varma, 1972) indicated that cannabis use was a factor in about 3% of patients hospitalized with a psychosis over a 10-yr period. This appears to be at least twice the estimated prevalence of regular cannabis use in the general population (Mohan, this volume), although some surveys of limited regions have indicated higher levels of general use.

Persons and Groups at Special Risk

Those Most Likely To Use Cannabis

Studies in developed countries have generally indicated that use of cannabis is greatest among early school drop-outs, young persons (under 25), males, those whose friends use cannabis, the military, criminal offender groups, venereal disease and casualty ward patients, some groups of psychiatric patients, and users of alcohol and other drugs (Smart, this volume). Some, but not all, studies have shown users to have more signs of psychopathology than nonusers; as cannabis use becomes normative behavior in some countries, this difference will probably disappear.

In developing countries it is more difficult to generalize, since cannabis is much more culture-bound, and varies widely even within the same country, according to the locale, religion, language, socioeconomic status, and sex of the groups studied (Mohan, this volume).

Those at Risk of Adverse Effects on Health

Because of the paucity of proper epidemiological studies on general populations, it is difficult to draw any firm conclusions about special risk factors. However, observations on samples of selected subpopulations suggest characteristics that may predispose users towards adverse effects.

One such factor is age. Pre-adolescent and adolescent users may be particularly vulnerable because those who begin use early in life may be more likely to become heavy users, and risk is generally related to total exposure. However, older patients with cardiovascular or pulmonary disease and other physical vulnerabilities, and those in whom the typical subjective effects of the drug are unfamiliar and unwelcome, may also be at special risk of adverse reactions even when the drug is used therapeutically.

People with pre-existing mental illness, and those who use other drugs concurrently, appear to be at greater risk of cannabis-precipitated psychiatric problems (see Section 7: Psychiatric Effects of Cannabis Use).

Cultural and socioeconomic factors may influence the probability of either occurrence or definition and identification of adverse effects, especially those related to emotional or cognitive functions. For example, impaired cognitive function is more likely to be recognized in university students or in airline pilots than in agricultural laborers or in other groups for whom intellectual tasks are not important. Urban users also appear to differ from rural users in developing countries in that they consume more cannabis and alcohol and that they are more likely to recognize impairment of perceptual and intellectual abilities (Mohan, this volume).

In general, it can be predicted that risk of adverse reactions depends upon a complex interaction of dose, individual physical and psychic vulnerabilities, and the social-cultural matrix in which the use occurs.

9. GENERAL CONSIDERATIONS

Throughout the previous sections, several important considerations have recurred consistently in the discussion of various adverse effects.

Dose-Response Relationships

Pharmacokinetics of THC

When inhaled in smoke, THC is absorbed rapidly from the lungs. Peak blood levels are reached within minutes of the beginning of smoking, and decline very rapidly to about 5%–10% of their initial level within one hour, even though the subjective symptoms of intoxication may persist for 2–3 hr and the objective signs, even longer (Jones, 1980). After oral administration, an equivalent dose of THC is absorbed more slowly, producing a less intense intoxication with a longer latency of onset and a longer duration than after smoking. The decline of blood levels of THC is due to rapid conversion of THC (mainly in the liver) to the psychoactive metabolite 11-OH-THC and numerous other metabolic products of little or unknown biological activity (Gudzinowicz *et al.*, 1980). THC and its metabolites are also rapidly sequestered by the fatty tissues. These compounds are then released back into the bloodstream over a period of several days; this phenomenon slows the elimination of cannabinoids from the body. In experienced users, the terminal half-life of THC (a measure of the rate of biotransformation and elimination) is 19 hr, and of its metabolites about 50 hr (Hunt and Jones, 1980). In the human, elimination of the metabolites occurs mainly through the feces, although detectable amounts are also present in urine.

Correlation of cannabis-induced effects with blood levels of THC. Because of the rapid sequestration of cannabinoids into fatty tissues, the tissue:blood ratio of these compounds is not constant. Unlike the situation with alcohol, one cannot expect the blood levels of THC to be a good predictor of biological effects (Jones, 1980). In the absence of tolerance, brain levels of psychoactive cannabinoids in the appropriate but as yet unknown subcellular fraction would provide the only estimate that could be expected to correlate with behavior. Measures of blood levels of THC may have some value, however. If, for example, the relevance of different routes of administration, or patterns of use, to peak or average blood levels can be established, blood level determinations may be more reliable than estimates of administered dose for the cross-cultural comparison of adverse effects in heavy users (Petersen, 1979).

Relevance of tissue sequestration to toxicity. Because of the sequestration of cannabinoids, THC or its biologically active metabolites could theoretically accumulate in fatty tissues during chronic or intermittent administration (Jones, 1980). This accumulation would not be measurable by determinations of blood levels of cannabinoids, and has not, as yet, been demonstrated in human tissue samples.

Although a slowly cleared drug is not necessarily more toxic than one rapidly eliminated, the slow clearance will have the effect of prolonging drug exposure, thus enhancing any toxicity that the drug may inherently possess. The irregular dose and administration schedules employed by most cannabis users make accurate determination of actual drug exposure almost impossible.

In humans, cumulative behavioral or physiological effects have not been demonstrated under conditions of controlled administration of up to three months duration, although the simultaneous development of tolerance may have masked this phenomenon (Jones, 1980). In animals, cumulative toxicity, as manifested by delayed lethality and the sudden appearance of neurotoxicity after several weeks of treatment (Luthra *et al.*, 1976), has been observed at doses relevant to those consumed by human chronic users. The possible occurrence of cumulative toxicity in humans, therefore, is a question that should be examined.

Structure-Activity Relationships

There has been considerable research into the biological activity of naturally occurring cannabinoids and their synthetic analogs (Mechoulam *et al.*, 1980). Many studies were designed to assess the potential therapeutic efficacy of these substances (Cohen, 1980). Of the major cannabinoids, only THC has significant psychoactivity. Several other cannabinoids, however, demonstrate immunosuppressant activity in the mouse (Munson and Fehr, this volume), cause endocrinological and testicular disturbances in the rat (Bloch, this volume), and inhibit the synthesis of macromolecules *in vitro* (Munson and Fehr, this volume). Thus it appears that the mechanism of the psychoactive effect of THC can be separated from those of some of its other pharmacological effects. Also, if the other major cannabinoids are present in high concentrations in plant material with a low THC content, they may contribute significantly to the spectrum of cannabis-induced immunological and endocrinological toxicity.

Drug Interactions

A third major consideration in the relationship of dose to effects is that of drug interactions. The latter, like tolerance, can be explained by dispositional mechanisms (i.e., related to the metabolic fate of the drug in the body) or by functional mechanisms (i.e., related to the manner in which drugs produce their effects), or by a combination of both.

Interactions between cannabis and other drugs and chemicals in the environment should be expected, but their magnitude and health consequences cannot, in most cases, be specified now. Our understanding of the pharmacology of cannabis is only sufficient to say that interactions with a wide variety of licit, illicit, and therapeutic drugs, and probably with almost all chemicals, can occur in principle, and often do occur in fact.

We know that it is unusual for someone to use cannabis regularly without using other drugs concurrently. For example, in North America, cannabis is commonly combined with tobacco and alcohol, and less frequently with cocaine, phencyclidine, and many other drugs (Smart, this volume). In some other parts of the world opium is often used concurrently with cannabis (Mohan, this volume). The drugs which are combined, and their doses, vary with age, culture, country, socioeconomic status, availability, and many other factors not well characterized in controlled surveys.

We know from a small number of studies that cannabis alters the effects of a number of other drugs (for example, alcohol, barbiturates, nicotine, amphetamines, cocaine, phencyclidine, and opiates) (Siemens, 1980). Similarly, the other drugs can alter cannabis effects. However, the precise nature of the alterations is difficult to predict. This is probably because of the complexity of the interactions. Cannabis is a mixture of many chemicals with varied pharmacology (Turner *et al.*, 1980). THC administered orally probably has different effects on the metabolism of other drugs than does smoked cannabis. This is because a cannabis smoker would be exposed to chemicals (i.e., enzyme inducers in smoke) capable of interacting with other drugs different from those that an oral user would be exposed to. CBD has more marked effects on metabolism of certain other drugs than does THC (Siemens, 1980). Simultaneous exposure to unrecognized environmental chemicals can confound the situation even further. Since cannabis, THC, or CBD can alter the bioavailability, metabolism, clearance, and distribution of other drugs or chemicals (Benowitz and Jones, 1977), interactions could occur by means of various mechanisms. Other drugs may similarly modify the fate of cannabinoids in the body.

Cross-tolerance and cross-dependence between cannabis and other drugs can theoretically also occur by functional (nondispositional) mechanisms. This might lead, for example, to a situation in which, because of metabolic interactions, blood barbiturate levels are elevated in a cannabis user; yet, despite this elevation, the effects of the barbiturate might be lessened because of cross-tolerance probably determined by functional interactions. Hence the prediction of behavioral consequences would be difficult.

In addition to producing drug interactions by altering shared hepatic enzyme systems important in metabolism, THC could potentially interact with other drugs because of competition for available binding sites on plasma and tissue proteins. The quantitative significance of such an interaction, if it occurs, is unknown.

In summary, one can only conclude that cannabis is likely to interact with many drugs so as to enhance, diminish, prolong, or shorten the effects of both cannabis and the other drugs. Thus the complexity of cannabis pharmacology and the paucity of adequate research studies in animals or humans makes precise predictions of health significance of drug interactions impossible. Some interactions may be mainly of interest to scientists trying to understand mechanisms of drug action; others (e.g., the delayed absorption of alcohol or slowed metabolism of anticonvulsants observed in cannabis users) (Benowitz and Jones, 1977) will without question have health significance. The well documented cross-tolerance and the possible occurrence of cross-dependence with many licit and illicit drugs make the prediction of health consequences even less precise.

Marked and serious drug interactions are often not recognized or appreciated by clinicians until a number of patients have been harmed. Although clinical data are hard to obtain from cannabis users, we know enough already to predict that such interactions *could* occur. Both laboratory experiments (human and animal) and adequate epidemiological and field studies are needed to define properly the nature and consequences of these interactions.

Tolerance

A final factor in the discussion of dose-response relationships is tolerance. The occurrence of this phenomenon, characterized by a loss of sensitivity to the effects of a drug, must be considered whenever a drug is given more than once, and thus is relevant to any study of chronic toxicity. Tolerance to most THC effects has been demonstrated repeatedly, both in animals and in humans (Jones, this volume). It will occur after administration by any route, but the rate of its development is increased if an attempt is made to maintain the blood level relatively constant (as by giving the drug orally or in frequent parenteral doses). The differential development of tolerance to various effects, together with the available pharmacokinetic data, suggest that the mechanism is more functional than dispositional (Jones, this volume).

Tolerance to some effects develops rapidly after administration of doses that many would consider surprisingly small. For many effects, tolerance disappears equally rapidly (Jones, this volume). There is a little more uncertainty as to the precise rate of disappearance of tolerance in different organ systems and in different species, since systematic studies on tolerance loss have rarely been done. The degree of tolerance that can develop is similar to that produced by some opiates. Many characteristics of tolerance to THC are similar to those of tolerance to opiates, nicotine, and alcohol (Jones, this volume).

The so-called "reverse tolerance" (an apparent increase in drug sensitivity after a few exposures to low potency cannabis), if it occurs at all, is likely due to conditioned responses linked to familiar cues, such as those related to smoking or to other environmental factors, which facilitate the production of drug effects as the user gains experience with the drug (Jones, this volume).

The significance of tolerance as a potential adverse effect is unknown. However, various dramatic and fundamental neurochemical and physiological changes occur along with the development of tolerance. Many of these can possibly be assumed to have implications for long-term health (Jones, this volume).

Some Parameters Affecting Self-Administration

Titration

There is some evidence that adverse reactions to cannabis are fairly infrequent in experienced users, in part because these individuals have learned to "titrate" their dose (Negrete, this volume). This means that they adjust their rate of smoking according to their subjective feeling of the degree of intoxication. This phenomenon is by no means unique to cannabis; it is common practice among users of alcohol, tobacco, cocaine, and other psychoactive drugs. Titration is not fully effective in preventing dysphoria, however, since even experienced users can suffer adverse effects after smoking cannabis, particularly when it is unexpectedly more potent than usual or differently constituted. Adverse reactions also appear to be more common after oral ingestion of cannabis than after smoking (Weil, 1970). This observation probably results from the user's inability to titrate an oral dose because of the long latency of onset of effects.

Tolerance and Physical Dependence: Their Relationship to Drug-Seeking Behavior

Dependence, both physical and psychological, can develop rapidly in animals and in humans who are exposed to cannabis at doses and frequencies that produce sustained THC blood levels for a significant period of time (Jones, this volume). Some components of the withdrawal syndrome are similar to those produced by opiates, and by alcohol and other sedatives, when they have been given for relatively short periods of time. Controlled clinical studies (Jones and Benowitz, 1976; Nowlan and Cohen, 1977; Georgotas and Zeidenberg, 1979) have shown a picture that includes disturbed sleep, anorexia, restlessness, irritability, sweating, chills, slight hyperthermia, nausea, muscle spasms, tremor, diarrhea, and intestinal cramps. In controlled experiments, subjects first experienced symptoms about four hours after their last oral drug administration. The reactions peaked at about eight hours and had largely dissipated by the third postdrug day. The onset of symptoms corresponded closely to the period when THC blood levels were dropping rapidly.

Other studies (Miles *et al.*, 1974; Rossi *et al.*, 1974) using different designs have failed to confirm all of these findings although some postdrug irritability was reported. The prevalence of these symptoms among populations of cannabis users is unknown. Although some symptoms of cannabis withdrawal resemble those associated with withdrawal from other central depressants, no conclusions can be made with respect to common mechanisms at this point.

On theoretical grounds, tolerance and dependence could increase drug-seeking behavior in several ways:

1. Selective tolerance to the aversive effects of a drug might unmask the rewarding effects and thus increase the probability of use;
2. tolerance, by leading to more frequent use and larger doses, might strengthen the cycle of reward and repetition;
3. the progressive narrowing of interests and activities in dependent users (particularly in urban industrial societies) might make the drug occupy a steadily more significant role in everyday life, and give rise to secondary and conditioned mechanisms that would have the effect of increasing drug use (reinforcement);
4. abstinence symptoms, occurring during drug withdrawal, could generate a new reinforcement for use to alleviate the discomfort.

For the first three ways there is no information available specifically on cannabis, though the general principles derived from the study of other drugs (Cappell and LeBlanc, 1979) would be expected to apply equally to it. With respect to the fourth point, the observations cited above suggest strongly that mild to moderate withdrawal reactions can and do occur in some regular users, especially frequent users of high doses.

Principles of Experimental Design

Relevance of Animal Models for Predicting Toxicity in Man

Although some pharmacological effects can be measured directly in humans, it is evident that experimental assessment of all risk potential of cannabis use cannot be performed safely in humans. Therefore, animal models must be utilized. The resulting problems of extrapolating from animals to humans should be minimized by selecting those *in vivo* paradigms that are relevant to human physiological and pharmacological responses. It is also important that administration of cannabis products extend over a sufficiently long fraction of the animal's life-span to simulate use of cannabis for a period of years by humans. On the other hand, some animal life-spans (e.g., dog and monkey, 15–25 yr) are long enough that the investigator who wishes to use these species must have high motivation and longevity, and reliable long-term funding. If possible, the experimental designs should be comparable to current human practices such as the smoking of high potency cannabis preparations mixed with tobacco, or the combination with other drugs, and the use of oral and other routes of administration.

Advantages and disadvantages are inherent in each potential animal model. For example, several rodents can be exposed simultaneously to the smoke of the same marihuana cigarette(s). Larger animals must be exposed to the smoke of individual samples of a batch of cigarettes that may differ considerably from each other in physicochemical properties. Physiological disposition of drugs also varies among species but sufficient basic data exist on these differences to permit appropriate interpretation of differences in time of appearance, intensity, and duration of responses in laboratory animal species and in humans. It must be noted, however, that the results from some animal models (such as immunosuppression in the mouse) may be extrapolated to humans more reliably than those from others (such as placental transfer of drugs in rodents).

In cannabis research, the strongest evidence supporting the relevance of animal models is the consistent dose range over which similar pharmacological events, including certain behavioral changes, can be observed and measured in rodents and nonhuman primates after administration of the drug by several different routes (see, for example, Rosenkrantz and Braude, 1976). These drug-related aberrations observed in animals have been produced by inhalation or oral doses that are relevant to those used by man. Indeed, circulating blood levels of

THC associated with these effects have been similar in animal models and humans. Even such a phenomenon as the characteristic biphasic response to cannabinoids (CNS-stimulation/inhibition) has been observed in both animals and man (Rosenkrantz, this volume).

Optimal Design of Toxicological Studies

Apparent contradictions in the experimental literature are often difficult to interpret because of differences in experimental design. For this reason, it seems desirable to specify some basic requirements for soundness of toxicological studies. This section is not intended to be comprehensive or definitive, but identifies a few areas of special concern.

The design of toxicology studies should be such as to permit clear identification of the organs which undergo dose-dependent morphological, physiological, or biochemical disturbances. For this purpose, the ideal study would evaluate the drug effects on *all* organ systems at several dose levels. Subchronic and chronic toxicological studies should be performed in both sexes of several species of experimental animals including rodents and nonhuman primates. The subchronic study should be long enough to identify appropriate dose ranges and to point to specific target organs or systems that would be investigated in greater detail in the chronic study. The chronic study must be of reasonable length as discussed in this section above, especially to provide sufficient time to determine the potential for carcinogenicity. Both inhalation and oral routes of administration should be used. Inhalation studies should use a standardized smoking system to assure direct inhalation of smoke. For inhalation studies, the cannabis preparation should be derived from standard marihuana cigarettes with sufficiently high concentration of cannabinoids to deliver the desired dose of active substance with a minimum amount of carbon monoxide. Control cigarettes should consist of the same marihuana extracted in a manner designed to maximize the difference in cannabinoid content while minimizing the loss of other constituents. A group of animals receiving the smoke from an appropriately standardized tobacco should be included so as to facilitate comparisons between the results from different laboratories.

Oral administration should be accomplished by feeding unless the drug preparation reduces food intake, in which case gavage should be used. The cannabis preparation used for oral administration should simulate as closely as possible those which are in widest use throughout the world. Adequate dose/response data must be provided, over a range extending up to the estimated maximum tolerated dose.

The toxicological study should not only assess the standard parameters such as growth rate, food and water consumption, hematology, clinical chemistry, urinalysis, and histopathology but should make every attempt to evaluate the functional aspects of the major organs and body systems. The pulmonary system should be evaluated at regular intervals in the larger animals by measuring respiratory parameters such as rate, volume, and blood gases. Behavioral effects should be monitored at regular intervals by accepted operant and nonoperant methods. The cardiovascular system should be monitored regularly, primarily by EKG. Liver and kidney function tests should be followed at regular intervals. In the larger animals, simple immunological assays should be carried out during the study but detailed humoral and cell-mediated immune responses need to be tested only at the end of the subchronic (90 day) study. Evaluation of the endocrine system should be carried out at regular intervals and should include measurement of plasma levels of appropriate hormones.

Animals should be set aside for use in three-generation reproductive and teratogenicity studies.

Carcinogenicity should be determined by appropriate histopathological studies of tumors and tissues at time of necropsy.

Selection of Subjects and Designs for Clinical Experiments

Most individuals who have participated as subjects in cannabis-related research in North America and Western Europe have been healthy young adult males who generally have used cannabis for five years or less. Most were students from middle- to upper-class socioeconomic backgrounds. Therefore some data obtained in these studies may have limited generalizability to females and to individuals who use cannabis in other social, economic, and cultural environments. Cross-cultural generalization of the findings appears to be very limited, since studies of cannabis use and effects in countries such as Egypt, Jamaica, India, and Greece involved subjects who were older, less affluent, and who used higher dosages and for longer periods of time than research subjects in North America. Since patterns of dosage (both amount of drug and frequency of administration) are, in part, culturally dependent, comparisons between cultures are especially difficult (see this section: Dose-Response Relationships).

Many problems in design of cannabis studies are similar to those encountered in research with other psychoactive drugs. Many studies of experimental administration of cannabis have not employed placebo controls, although it should be emphasized that effective placebo control in chronic studies with highly discriminable psychoactive compounds such as cannabis, especially with experienced users, is difficult. Interpretation of results has often been rendered difficult by factors such as variable and unstated expectations or biases of subjects and experimenters, variations in criteria for defining chronicity and dosage, and variables associated with set and setting. Important controls for basic variables (e.g., drug use other than, or in addition to, cannabis) have been hard to achieve in research on humans, except in experimental studies in monitored research ward environments. Only a few studies have provided subjects with specific incentives for cooperation, or special compensation for achieving best performance during the assessment of cannabis effects on behavior (see, for example, Cappell and Pliner, 1973). In some studies, subjects (all cannabis users) were apparently self-motivated to perform well, in order to establish the absence of cannabis-related adverse effects (Kalant, 1969). Since virtually all studies have employed volunteer subjects, there remains some question as to whether these healthy individuals are truly representative of the general population of cannabis users.

Sex Differences

There have been very few controlled administration studies in human females, or examinations of sex differences in response to cannabis in animals. Male animals demonstrated a different pattern of behavioral toxicity, and were more susceptible to delayed lethality than the females (Luthra *et al.*, 1976). Otherwise the results have revealed no overall pattern. In the past, for reasons related to U.S. Food and Drug Administration policy, or equivalent policies in other countries, there have been practically no studies of the effects of cannabis administered experimentally to human females, and none involving chronic administration.

Discussion of the Nature of Proof Required To Establish a Drug Effect

The question often arises as to the rigor of evidence or standard of proof required to substantiate statements about the effects of cannabis use. Under more readily controlled circumstances, namely, *in vitro* and in animal *in vivo* experiments, a cause-effect relationship in the action of a cannabis constituent on some biological endpoint (metabolic, molecular, physiological, etc.), may be considered established if the following three requirements are met:

1. molecular or structural specificity of the constituent causing the effect;
2. an appropriate dose-response relationship, both with respect to range and slope; and

3. absence or inhibition of effect by neutralization or removal of the constituent.

In addition, in *in vitro* experiments the relevance of effect would need to be established by comparing the required drug concentration *in vitro* to that found *in vivo*.

The assessment of clinical evidence, however, has posed many more problems. Historically, the most common sequence of development of knowledge about a new clinical problem has included the following steps: recognition of individual cases; study of series of cases in comparison with clinical control groups; epidemiological study of incidence and prevalence in defined populations; inferential identification, from the foregoing data, of possible etiological factors; and experimental demonstration of probable mechanisms. The value of the initial steps, despite the obvious limitations of the information they provide, has not been questioned in relation to other clinical problems. In contrast, very high standards of proof are sometimes demanded from evidence concerning cannabis (see, for example, Grinspoon, 1977). It is instructive to make comparisons with the study of effects of other drugs, such as tobacco or alcohol. With these drugs, "risk factors" have been freely identified, although full causality has not yet been established. Nevertheless, such risk factors deserve and receive serious attention with respect to the latter drugs. It is puzzling that the same reasoning is often not applied to cannabis.

In some cannabis research on humans there are numerous constraints which are difficult to overcome directly. For example, in many of the epidemiological, laboratory, or clinical quasi-experimental studies, it seems that researchers can demonstrate relationships only by establishing statistical association. Whether in the area of cannabis research, investigations of other drugs or in other less complicated areas, the research worker more often than not is faced with a variety of possible interpretations of the findings, due to the multiplicity of variables that arise particularly from dealing with human beings. Moreover, in field studies comparing matched groups of users and nonusers, it must be remembered that it is, by definition, impossible to determine a drug effect on the variable with respect to which the groups are matched. For example, if the users and controls are matched with respect to socioeconomic status, any possible effect of drug use on socioeconomic performance is automatically excluded.

Therefore, the researcher can only proceed towards formulating new hypotheses about possible mechanisms or processes involved, and progress by what is usually labeled the method of successive approximations, i.e., gradually narrowing the range of possible interpretations.

This method is followed in all endeavors in science, cannabis research included. To provide rigid proof of causality in such investigation is logically and theoretically impossible, and to demand it is unreasonable.

10. SUMMARY

The acute use of moderate doses of cannabis produces a state of intoxication. This is associated with a dose-related impairment of the ability to drive a car or operate complex machinery. In some situations, the user may not feel the desired euphoric state but rather may experience a short-lived dysphoric reaction which can range in intensity and character from mild anxiety to an acute psychosis. Other acute physiological effects are also transient and do not appear to be of major significance in individuals with no pre-existing disease.

Intermittent use of low-potency cannabis is not generally associated with obvious symptoms of toxicity. Daily or more frequent use, especially of the highly potent preparations, can produce a chronic intoxication which may take several weeks to clear after drug use is discontinued. The seeming inconsistency of this observation throughout the world may reflect differing exposures to THC because of the large variation of potencies and smoking techniques, as well as different cultural preferences for the route of administration.

Respiratory toxicity is observed in heavy users and is probably related to smoke components other than THC. Therefore its severity may depend more on the smoking techniques employed by the user and the combustion properties of the material, than on the THC content. Cannabis effects on the hormonal, reproductive, and immunological status of these users is, as yet, unclear.

Chronic administration of cannabis results in the development of tolerance to a wide variety of the acute drug effects in both humans and experimental animals. Though scientific opinion is more divided on the question of dependence on cannabis, there is now substantial evidence that at least mild degrees of dependence, both psychological and physical, can occur.

Some individuals may be particularly susceptible to the effects of cannabis for a variety of reasons. Adolescents who are undergoing rapid developmental change and elderly populations with decreased rates of drug metabolism, increased prevalence of disease and a more conservative and less flexible mental set may be more sensitive to the effects of cannabis and other drugs. The symptoms of patients with a variety of diseases including various forms of mental illness, diabetes, cardiovascular disease or epilepsy may be exacerbated by cannabis use. Interactions with a variety of substances including tobacco and alcohol may also potentiate the observed effects.

The epidemiological studies necessary to assess the frequency of adverse effects and to relate their occurrence to factors such as potency and amount of cannabis used, length of exposure, set and setting have not, as yet, been conducted. The low prevalence of adverse effects observed in field studies of small numbers of heavy users suggests that the adverse effects described in many of the clinical reports occur relatively infrequently in these carefully selected populations. Given that millions of individuals are now using the drug, even relatively infrequent but serious adverse consequences could be of public health significance.

The results of experimental studies in animals have consistently demonstrated toxicity at doses comparable to those consumed by the human who smokes cannabis several times per day. Respiratory toxicity, CNS dysfunction, endocrinological disturbances, reproductive deficits, and immunosuppression have all been observed after treatment with THC or cannabinoids in experimental animals. Most, but not all, of these effects disappear when treatment is discontinued. *In vitro* studies have also been used to demonstrate cannabis-induced cytotoxicity. The results of these experiments are, for the most part, qualitatively consistent with the *in vivo* observations, and may provide valuable information about the mechanisms of action of the cannabinoids and other plant components or products of pyrolysis.

11. RECOMMENDATIONS FOR FUTURE RESEARCH

Based on a discussion of the available information on cannabis toxicity and the lack of relevant data in certain key areas, several recommendations for future study were reached. A comprehensive understanding of any biological phenomenon almost always demands the synthesis of information derived from a variety of experimental designs. Therefore, it is important that no single "best" scientific design be recommended. On the contrary, it is recognized that a broad, integrated approach employing different techniques is most likely to provide the information needed for valid conclusions regarding the adverse effects of cannabis on health and behavior.

1. As outlined in Section 1, there is a lack of consensus on what constitute the criteria for "social" or "problem" use. Standardization of terminology with respect to patterns of use would greatly facilitate the comparison of clinical reports. There should be a search for "biochemical markers" to identify heavy users (such as the changes in transferrin or abnormal hemoglobin A used to identify recent heavy

users of alcohol) that could be used as an objective measure of hazardous use.

2. Many general considerations were raised. There is an obvious need to relate biological responses not only to the doses given but also to blood and relevant organ levels of THC and its major active metabolites and to the duration of exposure to such levels. For this reason, further studies of the pharmacokinetics (both acute and chronic) of THC and other cannabinoids are indicated. It is important to explore the contribution of THC to biological effects, as compared to the possible role of other cannabinoids and of other substances contained in the cannabis preparations.

3. Wherever possible, the effects of cannabis should be compared with those of equieffective doses of other drugs with respect to some common action, so that cannabis toxicity can be considered within the context of toxicity of psychoactive drugs in general. This will indicate which effects are specific to cannabis and which are common to many drugs.

4. It must also be emphasized that, with the exception of a few case reports and limited experimental studies, almost all information so far obtained has emerged from observations of healthy mature males. This limits the extrapolation of results to other segments of the population. For example, there is virtually no information on the effects of cannabis on women. Because of the increasing prevalence of use by women and the evidence of sex differences in the biological response to many other drugs, studies in this area are vitally necessary.

5. Other groups may, for various reasons, be particularly at risk for the appearance of adverse consequences. The effects of cannabis on children and adolescents, a group undergoing rapid physical and psychological maturation, should be intensively studied since, in some countries, cannabis use is already very high and increasing rapidly. Effects on academic achievement, and on endocrinological profiles during puberty, are areas particularly deserving of study.

Based on evidence from animal studies, it is also recommended that children exposed *in utero* to cannabis should be examined postnatally for signs of impaired growth and delayed maturation, and for long-term health and behavioral problems.

It is possible that cannabis is producing serious but as yet unrecognized toxic effects on persons with underlying psychiatric, pulmonary, cardiovascular, gastrointestinal, allergic, and dermatological disease, or with pathological or therapeutically produced immunosuppression.

Greater attention should be directed to the problem of cannabis-induced precipitation or exacerbation of these disorders.

Because of animal experiments suggesting that nutritional status may to some extent influence the magnitude and nature of the drug-induced effects, the relationship between poor nutrition and various cannabis-related effects should be studied.

Conversely, efforts must be made to identify special risk factors in those experiencing adverse effects, so that additional groups at risk may be identified.

6. There were also suggestions aimed at improving the quality and reliability of the data available from clinical and experimental studies. Case reports are still necessary to identify rare drug-induced effects, and to confirm the existence of other previously reported signs of toxicity. More complete and consistent descriptions of clinical observations, including the extent and pattern of drug use (cannabis and other drugs) accompanied if possible by objective testing, would add to the value of these reports. There is also a need to identify, in the community, those individuals who may not be seeking medical attention for adverse effects. These "out-reach" studies would provide a more accurate estimation of the prevalence of the relevant symptoms than can be provided by case reports alone. More systematic enquiring and reporting with respect to drug use by clinic and hospital patients would also assist in the assessment of the prevalence of adverse effects.

The data from carefully designed retrospective studies should not be underestimated. By means of controlled retrospective studies, the apparent over-representation of certain characteristics (such as age, sex, and pre-existing psychopathology) among patients presenting complaints related to drug use can be assessed. Since adverse drug effects are more likely to be found in individuals who are identified as "patients," i.e., who present with complaints, than in healthy users without complaints, it would be informative to apply objective measures such as various physiological and psychological test batteries to groups of patients with complaints rather than only to groups of healthy drug-using volunteers.

In the past, a large number of cross-sectional studies of cannabis users matched with nonuser controls have provided information on the drug's possible toxicity. In view of the difficulties in designing a prospective study, a thorough reassessment of previously studied subjects presents certain advantages, despite the difficulties of tracing some of the individuals involved. The subjects would be older and would have had longer cannabis exposure. Thus they would be more likely to show cannabis-related symptoms. Previously made measurements could be repeated, and recently developed techniques could be employed to provide additional data.

Obviously an ideal approach is that of the controlled study of experimental administration. In this manner, confounding variables such as diet and concomitant use of other drugs can be eliminated. In such settings the subjects can also be treated with dignity and safety. From the animal studies, however, it is apparent that long-term exposure is needed for the production of adverse chronic effects. Experimental administration studies in humans should not be used to determine long-term toxicity. Optimally, methods should be developed for performing both cross-sectional and experimental administration studies without the need for hospitalization.

7. Several types of epidemiological studies are suggested to (a) determine the prevalence and trends of cannabis use in general and special populations throughout the world, and (b) to determine the frequency of adverse reactions, especially those requiring medical treatment among groups of cannabis users. The prevalence-of-use data should include information on the dose (in terms of THC content, route of administration, and frequency of use). This would include worldwide assays of potencies of various illicit cannabis preparations. The surveys of frequency of adverse effects should help to separate the influence of various factors such as frequency of use, experience with other drugs, and pre-existing psychopathology. There is also a special need for studies of the frequency of respiratory, hormonal, cardiovascular, and other nonpsychological adverse consequences of cannabis use. Because of the experimentally observed carcinogenic and mutagenic potential of cannabis smoke, possible signs of increased incidence of cancer must be monitored carefully in groups of heavy users. Analysis of ongoing epidemiological data such as hospital and emergency service visits, treatment referrals, etc., is very important and should be continued.

8. Encouragement should be given for prospective studies of potential user groups, including observations of baseline (predrug) health status and the occurrence of cannabis-related toxicity during and after periods of heavy use. On a large scale they are difficult to design and expensive to conduct. However, this approach remains the best technique for establishing, in humans, directness of connection between drug use and an observed effect, and for determining the relationship between recorded levels of use and the prevalence of adverse effects. Thus attempts should be made to conduct such studies. Less optimally, efforts

could be made to extract pertinent data from prospective studies being conducted for other reasons.

9. The optimal designs of experimental studies of toxicology have been outlined in Section 9. It is recommended that adequate investigations using a variety of species, doses, routes of administration, and lengths of exposure (including full-life studies) be performed to evaluate cannabis effects on all organ systems and to assess potential teratogenicity, mutagenicity, and carcinogenicity. Research on endocrine and reproductive functions should also include serial measurements of transplacental cannabinoid transfer throughout gestation, and estimations of cannabinoid concentrations in breast milk and nursing pups. Further experiments should be encouraged to elucidate the cellular and molecular mechanisms of action of cannabinoids and to analyze cannabis smoke action in a variety of *in vitro* systems.

10. On the behavioral level, several recommendations have been made. Suggested psychosocial studies include examinations of the influence of legal controls on patterns of cannabis use and on the drug-induced behavioral response of the user. For example, observations of the user's social interactions, such as peer relationships or family structures and attitudes, may provide data related to reasons for the initiation and maintenance of cannabis self-administration, and may provide independent assessment of the user's behavior while in the intoxicated or nonintoxicated state.

Behavioral studies should include measures of psychomotor and perceptual functions that would be expected to affect one's ability to drive a motor vehicle or otherwise perform safely in the work place. A replication of the reported research on driving on city streets is necessary to confirm earlier results. The hazards of operating complex machinery while intoxicated should be assessed, especially in those countries with newly introduced mechanized farming where rural cannabis use is traditional. Wherever possible, cannabis-induced effects on night driving should be examined, as well as interaction with alcohol and other drugs, and the potential development of tolerance to cannabis-induced driving impairment.

Residual CNS toxicity as a result of long-term cannabis administration must be examined in greater detail. In animal models, the possible contribution of other individual or environmental factors, such as innate intelligence or environmental stimulation, to cannabis-induced learning impairment, EEG changes and histopathology could be assessed. In humans, a careful longitudinal study with verified drug-free periods before testing would help to determine whether or not residual toxicity occurs. The question of an absence or redirection of motivation in heavy users must be examined in greater detail. In addition, an exchange should be set up for autopsy brain bank samples and case-history information relevant to chronic heavy users, to provide material for *post hoc* analyses of brain in correlation with recorded levels of use.

11. Additional observations are needed to identify the intervening pharmacological, neurophysiological, and psychopathological factors underlying acute panic and paranoid states and other cannabis-related psychiatric disorders. A comparison between cannabis-related psychiatric disorders and those produced by other drugs, as well as functional disorders, would also be profitable. A controlled study of the intervening etiopathogenic factors underlying spontaneous recurrence reactions ("flashbacks") could be of assistance in the elucidation of the mechanism(s) related to these symptoms.

Specific treatment procedures should be developed to minimize the potentially severe dysphoric states that can occur as a result of the therapeutic use of THC and synthetic cannabinoids. Such studies might not only be of value to patient care, but also shed light on the mechanisms of drug action.

12. Immunological studies should include epidemiological investigations of the prevalence, severity, and duration of selected infectious diseases in populations from which data are readily available and in which use is known to be high (e.g., students, military personnel). For example, the question of a possible cannabis-related decrease in the immune response to herpes simplex should be studied in a group of cannabis users known to be infected with herpes.

13. Because of the multiple drug intake of many cannabis users, better and broader drug interaction studies (especially regarding behavioral impairment, pulmonary and liver toxicity) are necessary. These should be conducted with both licit and illicit drugs such as caffeine, nicotine, psychotherapeutic agents, and antihistamines. Data from pharmacokinetic experiments will be helpful in the interpretation of drug-interaction phenomena.

14. The development of tolerance to, and dependence on, drug effects, whether they be therapeutic or adverse, is a phenomenon that must be considered in the evaluation of any chronic psychoactive drug effect. More sensitive measures are needed for the identification of dependence, the delineation of time course of acquisition and particularly of the disappearance of tolerance, and its implications with respect to function. The relationship of tolerance, physical dependence and

drug-seeking behavior must be established, both for cannabis and for other concurrently used drugs.

Since increasing numbers of cannabis users are now presenting signs of dependence, research must be conducted on methods for treating this problem.

15. Finally, adverse health effects are better prevented than treated. The development of educational programs designed to discourage hazardous cannabis use should be encouraged, and the results of such programs evaluated.

In brief, the obvious need for further cannabis research has been demonstrated. Because of the cannabis-related problems throughout the world, it is imperative for agencies such as the WHO to alert national governments and international agencies to this need. The benefits of cooperation between developed and developing countries in this area would be mutual.

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Clinical Toxicology of Cannabis Use

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1. INTRODUCTION

Clinical reports of toxicity in cannabis users have often engendered considerable controversy since observations of patients cannot be interpreted in the same manner as experimental studies. These observations, however, are extremely important to the body of knowledge on cannabis because they deal with the realities of health care and treatment. In addition, the public wants to know whether cannabis smoking can cause someone to become "sick" and require medical treatment. The credence of clinical reports on toxicity appears to be increasing, since reports dating back to the *Indian Hemp Drugs Commission, 1893–1894* (1969) are now being validated by various research methods.

This paper reviews nonendocrine, nonimmunological, and nonbehavioral toxic effects of cannabis as observed in clinical settings. Major attention is directed at problems that clinicians detect in populations that use cannabis. Possible toxic effects that have received little attention in scientific and lay literature are reviewed.

2. REPORTS OF TOXIC EFFECTS BY USERS

Clinical Complaints

Analysis of clinical toxic effects of cannabis begins with the review of studies of user-reported side-effects significant enough to warrant clinical treatment (Tennant, 1974). Clinicians in describing toxic effects of cannabis have usually detected complications because a patient complained about a problem and temporally related it to cannabis use. Included among the clinical complaints are certain respiratory, cardiovascular, gastrointestinal, dermatological, neurological, or allergic effects.

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TABLE 1

Common Clinical Presenting Complaints of Cannabis Users

- Abdominal cramps
- Chest pain
- Constipation
- Cough
- Diarrhea
- Dizziness or vertigo
- Dyspnea
- Headache
- Nausea and/or vomiting
- Rhinorrhea
- Sore throat

Table 1 lists the common complaints voiced by cannabis users seeking clinical treatment.

Nonclinical Surveys of Users

In at least three studies, cannabis users have been surveyed outside of clinical settings and asked whether undesired drug effects were experienced (Halikas *et al.*, 1971; Fisher, 1974; Tennant, 1974). Tennant (1974) surveyed 492 smokers of high potency hashish by anonymous questionnaire and found that 290 (58.3%) experienced one or more of the following undesired side-effects: bronchitis, 6.1%; sore throat, 24.8%; running nose, 8.7%; diarrhea, 4.7%; headache, 14.2%; emotional problems, 8.5%. In addition, 69 (14.2%) claimed they had to visit a physician at least once for an ailment caused by hashish. Sixteen (3.3%) stated that they needed to visit a physician five or more times for the hashish-induced ailment. Halikas *et al.* (1971) surveyed 100 regular marihuana users and found that a large proportion experienced, at least occasionally, unwanted behavioral or somatic side-effects. These included dizziness reported as occurring at least occasionally by 82% of the respondents, dyspnea (28%), headache (30%), periorbital edema (22%), nausea (9%), vomiting (2%), diarrhea (4%), and constipation (4%). Fisher (1974) reported that 13.9% of 530 Los Angeles marihuana users felt that they had harmed themselves in some psychological or emotional way, and 157 (31.8%) stated that they knew of someone else who they felt had been harmed by marihuana. Only 10 (1.9%) felt, however, that they had been physically harmed themselves by marihuana.

Effects of Toxicity on Use Rates

Even though there are few nonclinical surveys of toxic effects in populations of cannabis users, they are impressive in that they reveal that users frequently experience numerous unwanted toxic effects. These effects, albeit minor and not permanent in most cases, probably serve to limit cannabis use in the general population. The development of tolerance to such acute toxic effects as anorexia, nausea, abdominal distress, diarrhea, and stuffy nose was demonstrated in a closed-ward study by Jones *et al.* (1976), although tolerance to the effects did not apparently develop in all subjects. Cannabis use historically has never achieved the popularity of alcohol, nicotine, and caffeine use even in permissive cultures. Persons who tolerate the numerous acute toxic effects of cannabis are probably the only persons who are able to use the drug chronically. This factor undoubtedly contributes to the relative lack of toxic effects found in long-term users.

3. STUDIES OF CLINICAL TOXICITY

Types of Study

Three major types of study since 1970 have contributed to current knowledge of clinical toxicity: (i) evaluations of clinical subjects; (ii) short-term, closed-ward administration of marihuana; and (iii) field comparisons of chronic users with controls. To date, information gathered in all three types of study tends to be very consistent.

Systematic Evaluation of Clinical Subjects

Tennant *et al.* (1971) performed a systematic evaluation of U.S. Army soldiers in Europe who smoked large quantities of potent hashish over a period of several months. All temporally related their habit to one or more medical complaints which were severe enough for the users to seek treatment. Systematically, each patient was given a complete physical examination and a variety of laboratory tests. Respiratory ailments and slightly impaired pulmonary functions were found to be the primary toxic effects. No evidence of cardiac, hepatic, hematological, neurological, renal, or gastrointestinal toxicity was detected. Some subjects voiced gastrointestinal complaints or gave a history of aggravation of an allergic or dermatological disease.

Since this study, numerous clinical reports and other more sophisticated studies have confirmed these early observations.

Closed-Ward Administration Studies

There have been three closed-ward studies in which subjects were given regular marihuana doses for periods ranging from 21 to 94 days (Cohen *et al.*, 1976; Jones *et al.*, 1976; Mendelson *et al.*, 1976). The potency of the marihuana was low (less than 3% THC). Even with the low dosage and relatively short administration period, subjects showed a decrease in pulmonary function (Cohen *et al.*, 1976; Mendelson *et al.*, 1976). There was slight decrease of hematocrit value and hemoglobin in the Jones *et al.* (1976) study group, but this was believed to be due to a plasma volume increase. Just as in the systematic evaluation of clinical subjects by Tennant *et al.* (1971), no evidence of significant cardiac, hepatic, neurological, hematological, renal, or gastrointestinal toxicity was found in any of these closed-ward studies.

Controlled Field Studies

In an effort to compensate for methodological defects in systematic clinical evaluations and closed-ward administration studies, three controlled field studies have been conducted in Greece, Costa Rica, and Jamaica (Table 2) (Boulougouris *et al.*, 1976; Coggins *et al.*, 1976; Cruickshank, 1976). All three involved relatively small numbers of chronic cannabis users who had no clinical complaints and who were evaluated by history, physical examination, and a variety of laboratory tests. Subjects were matched with non-cannabis smoking controls. There was more bronchitis in Greek subjects and more postexercise hypoxia in Jamaican subjects than in controls, indicating the presence of subclinical pulmonary disease. Costa Rican and Jamaican smokers had more weight loss, and Costa Rican users had more gastrointestinal complaints than did controls although there was no consistent pattern. The Greek hashish users had slightly more peripheral neurological findings. Hepatomegaly, in the Greek study, was attributed to concurrent alcohol abuse. In one of the closed-ward administration studies, a low hematocrit value was found (Jones *et al.*, 1976), but the opposite was found in the Jamaican study. Like both the systematic clinical evaluation and closed-ward administration studies, the controlled field studies revealed no significant findings of cardiac, hepatic, neurological, hematological, renal, or gastrointestinal toxicity.

Methodological Defects in Toxicological Studies

A systematic evaluation of a clinical population (Tennant *et al.*, 1971) suffers from the methodological defects of having neither control subjects nor controlled administration of drug. The closed-ward administration studies are deficient in that low doses of low potency cannabis were administered for short periods of time. Subjects in the foregoing field studies were a special group of cannabis users. They regularly used

TABLE 2

Summary of Toxicological Field Studies of Long-Term Cannabis Users

Population	Length of Use	Number of Subjects	Control Subjects	Respiratory Abnormalities	Author
Adult male Greek hashish smokers.	40 years	44	Yes	Slightly more bronchitis than controls.	Bouloungouris *et al.*, 1976
Adult male Costa Rican marihuana smokers.	10 years	84	Yes	Chest x-rays normal.	Coggins *et al.*, 1976
Adult male Jamaican peasant ganja smokers.	15 years	30	Yes	Slightly more postexercise hypoxia in users.	Cruickshank, 1976

Cardiovascular Abnormalities	Gastrointestinal Abnormalities	Neurological Abnormalities	Author
None found	Hepatomegaly common but alcohol-related.	Slightly more peripheral findings than controls.	Bouloungouris *et al.*, 1976
Slightly lower blood pressure in users.	Users complained of more weight loss, indigestion, nausea, and abdominal pain.	None found	Coggins *et al.*, 1976
None found	None found	None found	Cruickshank, 1976

TABLE 2 (CONTINUED)

Renal Abnormalities	Hematological Abnormalities	Comments	Author
None found	None	One user with splenomegaly. More cigarette smoking and alcohol abuse in hashish smokers.	Boulougouris *et al.*, 1976
None found	Low hematocrit value in users.	Users used other drugs more and had more testicular atrophy.	Coggins *et al.*, 1976
None found	High packed cell volume in users.	Slightly lower weight in users.	Cruickshank, 1976

relatively moderate doses of cannabis for many years. These subjects obviously had developed tolerance to common toxic side-effects which many users experience and which appear to be unpleasant enough to cause cessation of cannabis use after minimal experience (Tennant, 1974). Most importantly, these same subjects were selected from a group that did not have any symptoms of illness or disease temporally related to cannabis which were severe enough to require medical care.

Although various toxicological studies have been quoted as substantiation of the relative lack of clinical toxicological effects, this interpretation is erroneous. The results produced in any of these toxicological studies described above could be identical to those of any study of tobacco smokers or alcohol drinkers if selection of subjects and the natural history of tobacco or alcohol use and abuse were not considered (Auerbach *et al.*, 1961; Lesesne and Fallon, 1973). A group of asymptomatic, non-clinical, chronic users of alcohol or tobacco could easily be selected in a field study and would be found to have suffered no toxicological effects when compared with nonusing controls. It takes approximately 20 yr of smoking a pack of cigarettes a day ("pack-years") to develop clinically significant respiratory disease (Auerbach *et al.*, 1961). One must regularly consume a significant dose of alcohol almost daily for approximately 10 yr ("wet-years") to develop cirrhosis of the liver (Lesesne and Fallon, 1973; Lelbach, 1974). Toxicological complications of tobacco, alcohol, cannabis, and all other drugs, are, therefore, the end result of a time-dose factor that must be exceeded before a toxic complication will occur. An understanding of this provides a simple but obvious explanation of why low potency doses of marihuana administered for a short time in a closed-ward setting may not produce any significant toxic effect. It may also explain why users consuming potent cannabis preparations (containing 5% to 15% THC) would be the most likely group to experience toxic effects severe enough to require clinical treatment (Tennant *et al.*, 1971).

At this time, little is known regarding the time-dose factor for cannabis, but when considered, it may explain minor differences in the findings reported in various toxicological studies.

4. PULMONARY EFFECTS

Historical and Present-Day Concerns

Since marihuana is usually smoked, the possible adverse effects on the lung and pulmonary function have long been of concern. This area has been reviewed by Petersen (1980) and the conclusions are discussed here. It is noteworthy that one of the earliest attempts to assess the health and social implications of cannabis use by the Indian Hemp Drugs Commission, 1893–1894 (1969) includes observations about its pulmonary effects that are surprisingly similar to more modern observations. For example, that *Report* mentions a possible value in the treatment of asthma because of the drug's "pulmonary sedative" qualities. However, it goes on to say that "long continued smoking . . . doubtless results in the deposition of finely divided carbonaceous matter in the lung tissues, and the presence of other irritating substances in the smoke ultimately causes local irritation of the bronchial mucous membrane, leading to increased secretion, and resulting in the condition which is described as chronic bronchitis in ganja smokers." The *Report* makes still another observation strikingly descriptive of present day marihuana use, viz.: "In ganja smoking . . . the inspiratory act is far greater and more prolonged, a larger volume of smoke entering the lungs than in cigarette smoking." Such deep inhalation of marihuana may well offset the typically smaller amounts smoked as compared with cigarette smoking. One indication of this is to be found in a study comparing marihuana and cigarette smokers which found that smoking less than one "joint" per day decreases specific airway conductance as much as smoking 16 cigarettes per day (Tashkin *et al.*, 1980). This change appeared to be due to increased resistance in the large airways. Although the ratio found needs to be confirmed by more extensive research, it suggests that the mode of marihuana inhalation and the way in which it is consumed may result in disproportionately adverse pulmonary effects as compared with those produced by modern tobacco cigarettes. Part of this difference may be accounted for by the fact that present day cigarettes are filtered and produce significantly lower levels of "tar" than was true in the past. Marihuana "joints" are unfiltered and virtually entirely consumed. Moreover, under conditions of ready availability there is some evidence that the number of "joints" consumed may approach that of tobacco cigarettes (as high as 10 or more per day) (Cohen *et al.*, 1976).

Clinical Reports

Several clinical studies of users have reported symptoms such as laryngitis, cough, hoarseness, bronchitis, and cellular change in chronic marihuana and hashish smokers, which resemble those of heavy tobacco smokers (Tennant *et al.*, 1971; Henderson *et al.*, 1972; Chopra, 1973). A study of American soldiers stationed in Europe showed that these symptoms were serious enough to induce some of the chronic hashish users to seek medical treatment (Tennant *et al.*, 1971).

Chronic marihuana smoking frequently precipitates bronchitis in adolescents (Waldman, 1970; Cugell, 1971; Louria, 1971), and Tennant *et al.* (1971) believe that a clinical finding of lower respiratory disease in a young adult or adolescent should raise immediate suspicion of marihuana abuse. A swollen uvula secondary to irritation by cannabis smoke may be a useful clinical sign suggestive of recent abuse (Tennant *et al.*, 1971).

Field studies of small numbers of chronic cannabis users in Jamaica, Greece, and Costa Rica (Table 2) found only limited evidence of lung pathology (Boulougouris *et al.*, 1976; Coggins *et al.*, 1976; Cruickshank, 1976). This may have been due to multiple reasons: (i) traditional users in those countries do not inhale cannabis smoke as deeply and retain it in their lungs as long as do American users; (ii) persons who found cannabis irritating to the respiratory tract probably chose to cease use long before complications occurred; and (iii) techniques to measure pulmonary function were not particularly sophisticated in these studies. Tashkin *et al.* (1976) found, by using sophisticated techniques, that after 59 days of daily marihuana smoking there was a decrease in mid-expiratory flow rate indicating significant airway obstruction.

Impairment of Pulmonary Defense System

The irritation produced by cannabis smoke appears to have a considerable adverse effect. Cilia which assist in moving inhaled dust and other small foreign particles from the lungs have been found to be injured by marihuana smoke. Following exposure to marihuana smoke, anti-bacterial defense systems in lungs of animals have been shown to be less effective against *Staphylococcus aureus*, a bacterium causing a serious form of pneumonia (Huber *et al.*, 1975). While similar effects have not yet been demonstrated in humans, it would be surprising if they did not occur and may be expected to be dose-related. The greater the amount and frequency of use, the greater the likelihood of adverse pulmonary and other consequences.

Cannabis Use With Pre-existing Pulmonary Disease

It appears hazardous for patients with pre-existing pulmonary disease to smoke cannabis. A 17-yr-old boy with chronic granulomatous disease smoked marihuana contaminated with Aspergillus and contracted the disease (Chusid *et al.*, 1975). Subsequent studies by these investigators revealed that cultures of street marihuana showed a high prevalence of Aspergillus and other fungi. Another case of aspergillosis occurred in a 27-yr-old marihuana smoker with a history of atopy, asthma, and bronchitis (Llamas *et al.*, 1978). Other reports describe worsening of respiratory symptoms in patients with pre-existing asthma and chronic bronchitis, on smoking cannabis (Henderson *et al.*, 1972; Lewis and Slavin, 1975).

Cancer Potential

Analysis of cannabis smoke, animal studies, and a recent report by Tennant (1980) suggest that cannabis may have significant lung cancer potential. Certain napthalenes, particularly benzopyrene, are known to be cancer-producing; benzopyrene is reported to be about 70% more abundant in marihuana smoke than in tobacco smoke (Novotny *et al.*, 1976).

One assay to determine the carcinogenic potential of tobacco tars is application of tobacco smoke condensate on mouse skin. Marihuana smoke condensate was applied to mice for five days by Cottrell *et al.* (1973). They observed metaplasia of the sebaceous glands, an effect that correlates well with carcinogenicity of the compound. Hoffmann *et al.* (1975) painted marihuana and tobacco smoke condensates on separate groups of mice for 74 wk. They saw tumors in both groups of animals, with a larger number in the tobacco group.

Using explants of human lung tissue exposed to either tobacco or cannabis smoke, the Leuchtenbergers (1976) found cellular abnormalities, and alterations in DNA content and in chromosome number. They then employed hamster lung explants because of their longer survival time and noted malignant transformation after exposure of three to six months to both tobacco and marihuana smoke. When the malignant cells were injected into mice, fibrosarcomas developed. Marihuana smoke produced the changes more readily than tobacco smoke. In this experiment, the smoke from both plants acted as a tumor accelerator, not an initiator, since the control group also developed malignant tumors over a 12- to 24-mo period.

Serious lung effects have been found in rats exposed to marihuana smoke in quantities producing blood cannabinoid levels similar to those of human daily users (Fleischman *et al.*, 1979). The animals were made to inhale smoke in a specially constructed apparatus at daily intervals for periods corresponding to one-eighth to one-half of their normal lifespan. Extensive lung inflammation and degenerative changes were found that were similar to but more severe than those produced by exposure to tobacco smoke.

The only human evidence of carcinogenic potential is a study of 30 U.S. Army soldiers stationed in Europe who smoked large quantities of hashish, experienced respiratory symptoms, and volunteered for bronchial biopsies (Tennant, 1980). All 23 smokers of hashish plus cigarettes had one or more pathological alterations consisting of atypical cells, basal cell hyperplasia, or squamous cell metaplasia. Two of seven hashish users who did not smoke tobacco showed such pathological changes. Three nonsmoker control subjects who volunteered for bronchial biopsy did not demonstrate any pathological abnormalities. The histopathological lesions found among the users were identical to those associated with the later development of carcinoma of the lung when it occurs in tobacco smokers.

Concurrent Cannabis-Tobacco Use

Smoking both cannabis and tobacco is a very common practice. Current evidence suggests that the combined use is additive or even supra-additive insofar as irritation, inflammatory reaction, or carcinogenicity is concerned (Tennant, 1980). It seems obvious that the inflammatory reactions and inhibition of macrophage activity would be at least additive when both substances are smoked. Therefore, it is in the subgroup of heavy tobacco and cannabis users that the first evidence of increased incidence or severity of pathologic changes and possibly cancer will likely be found.

5. CARDIOVASCULAR TOXICITY

Acute Effects

Cannabis is known to have significant cardiovascular effects and EKG changes may occur during acute intoxication (Savary *et al.*, 1974; Clark, 1975). A number of studies, however, in which cardiovascular dynamics were studied some time after administration of large doses of THC, indicate that cannabis produces only minimal if any EKG changes in young healthy subjects (Benowitz and Jones, 1975; Clark, 1975; Malit *et al.*, 1975). Nonspecific P or S wave changes are most commonly noted (Kochar and Hosko, 1973). Occasional premature beats may also occur. Tachycardia is the most common and prominent physiological response to acute doses (Schaefer *et al.*, 1975). Cardiovascular effects during acute intoxication appear to be temporary and of no clinical consequence in persons with a normal heart. No consistent and lasting changes in blood pressure have been found (Jones *et al.*, 1976).

Clinical Studies

Several studies have investigated the possible cardiotoxicity of cannabis use. To date, however, clinical trials have shown no EKG evidence of long-term toxicity (Benowitz and Jones, 1975; Nowlan and Cohen, 1977). One group of investigators studied 21 male, experienced marihuana users who participated in a 94-day in-hospital study of heavy marihuana smoking (Nowlan and Cohen, 1977). During 64 days of the study the subjects smoked one to three marihuana cigarettes per day. These investigators found a significant increase in heart rate after marihuana smoking, although it was not as clearly dose-related as had formerly been reported by others. They attributed the lack of a clear dose-response relationship to the tolerance that develops to the cannabis-induced cardiovascular effects during chronic exposure. Other changes observed in cardiac function were secondary to transient tachycardia and did not appear to be clinically significant. The field studies of long-term users in Costa Rica, Jamaica, and Greece did not disclose any cardiovascular abnormalities (Table 2).

Effect on Pre-existing Heart Disease

Cannabis, in all likelihood, does not have significant, long-term toxic effects on a normal heart, but it is clear that it is a potential danger to patients with pre-existing heart disease. In patients with already impaired heart function, use of cannabis may precipitate chest pain (angina pectoris) on exertion (Angelico and Brown, 1974; Aronow and Cassidy, 1975). Smoking either marihuana or high nicotine cigarettes decreases exercise performance prior to the onset of angina by increasing myocardial oxygen demand and decreasing myocardial oxygen delivery (Aronow and Cassidy, 1975). Marihuana, however, appears to precipitate angina more rapidly than tobacco cigarettes, and following less effort. Cardiovascular hemodynamics were evaluated by EKG (Prakash and Aronow, 1976). After marihuana smoking, stroke index and ejection fraction decreased, and carboxyhemoglobin levels were elevated. One case of pulmonary edema and myocardial infarction following marihuana use has been reported (Charles *et al.*, 1979). This case is disturbing since it occurred in a 25-yr-old male with no known history of pre-existing heart disease. Similar observations have been made in animals (Forney and Kiplinger, 1971).

In summary, it is clear that persons with heart disease would be wise not to consume cannabis. Further observations need to be made on the potential of cannabis to produce infarction.

6. GASTROINTESTINAL TOXICITY

Clinical Toxic Effects

The occurrence of diarrhea, abdominal cramps, and vomiting has been observed in laboratory animals administered cannabis products, and these symptoms are reported to occur frequently in humans using the drug (Halikas *et al.*, 1971; Tennant, 1974). They may be severe enough to induce users to seek medical treatment (Tennant *et al.*, 1971). In contrast, other reports indicate that THC may be an antiemetic compound (Borison *et al.*, 1978), and that in some individuals cannabis may produce constipation, rather than diarrhea (Halikas *et al.*, 1971; Burton, 1979). The explanation for these apparently contradictory reports may lie in differences of dosage, or in other circumstances surrounding the cannabis use.

The field study conducted on 84 Costa Rican chronic marihuana smokers showed that users had more weight loss and more complaints of indigestion, nausea, and abdominal pain than did controls (Coggins *et al.*, 1976). Cruickshank (1976) found a slightly lower weight in Jamaican ganja smokers compared with controls. In closed-ward administration studies, observations of weight gain were made during subchronic administration of marihuana or THC, but the subjects lost weight rapidly when drug treatment was discontinued (Greenberg *et al.*, 1976; Jones *et al.*, 1976). Despite the occurrence of gastrointestinal complaints that may even require symptomatic medical treatment, there is no evidence that cannabis produces any direct, long-term gastrointestinal effects in a normal individual.

Mechanism of Diarrhea

Nalin *et al.* (1978) found that cannabis reduces gastric acid secretion and renders the smoker more susceptible to *Vibrio cholerae* and *Escherichia coli* infection, which may result in aggravated diarrhea. In particular, the investigators believed that the cannabis user was particularly susceptible to traveler's diarrhea. This study is important since it provides a possible explanation for the diarrhea, abdominal distress, and

TABLE 3

Contraindications and Inappropriate Consumption of Cannabis

Contraindications	Inappropriate Consumption
Tobacco smoker	Sharing of cannabis product or paraphernalia
Alcohol abuser	Swallowing a cannabis product
Pre-existing allergy, skin condition, pulmonary disease, heart ailment, neurological disease	Intravenous injection
Traveler to foreign country	Regular use of high potency cannabis

weight loss that are commonly observed in chronic cannabis users (Tennant *et al.*, 1971; Coggins *et al.*, 1976; Mendelson *et al.*, 1976).

Inappropriate Use and Adverse Effects

Cannabis has been consumed in ways other than by a single person smoking a single portion of the plant, and these practices have often resulted in adverse clinical effects (Table 3). Abrahm (1972) reported a young man who contracted multiple intestinal parasites after sprinkling raw marihuana leaves on salads. Dassel and Punjabi (1979) encountered three patients who swallowed marihuana-filled balloons. Two of these individuals developed intestinal obstruction and the third experienced rupture of the balloon with subsequent nausea, dizziness and sedation severe enough to require hospitalization.

7. LIVER TOXICITY

Clinical Reports

Kew *et al.* (1969) performed liver-function studies on 12 regular cannabis users in England and found evidence of hepatotoxicity in eight.

Hochman and Brill (1971) found abnormal liver function in 10 of 50 chronic marihuana users, but attributed this to concurrent alcohol abuse. Boulougouris *et al.* (1976) found hepatomegaly to be more common in Greek hashish users compared with controls and also concluded it was due to concurrent alcohol abuse. Other investigators have studied clinical and experimental populations to verify the hepatotoxicity of cannabis but have not found any (Tennant *et al.*, 1971; Coggins *et al.*, 1976; Cohen *et al.*, 1976; Cruickshank, 1976).

Explanation of Diverse Findings

In addition to alcohol abuse, other explanations have been offered for the occasional finding of liver dysfunction in clinical populations. Drachler (1975) found that sharing a pipe of hashish among smokers was associated with transmission of hepatitis. Regardless of whether this mechanism is always the cause of liver dysfunction in cannabis users, prudence indicates that users should not share for fear of hepatitis transmission. Mellors (1974) suggested that lysosomes may be damaged by THC and result in hepatotoxicity. Shapiro *et al.* (1975) found that some marihuana users who developed antibodies to marihuana also had abnormal liver function, which suggests a possible adverse antigenic response. Since alcohol abuse has been very common in cannabis users who have demonstrated liver dysfunction, it is quite possible that THC potentiates the toxic effect of alcohol on the liver by virtue of an antigenic or lysosome destruction mechanism.

8. DERMATOLOGICAL EFFECTS

Considerable public controversy was evoked when Lubowe and Huss (1969) described two patients with seborrheic dermatitis and acne which improved with discontinuation of marihuana use. Since then, essentially no studies of the association between cannabis and acne have been reported although at least one clinical report describes three patients who temporally related severity of acne and seborrheic dermatitis to hashish dosage (Tennant *et al.*, 1971). This is a particularly complicated area to study, since acne most commonly occurs in an age-group with a high prevalence of cannabis use. Poor personal hygiene is prevalent among drug users and may be the factor most directly responsible for acne in this group. A direct effect of cannabis on sebaceous gland function cannot be ruled out, however, since Cottrell *et al.* (1973) found that marihuana smoke condensate has a significant pathological effect on the sebaceous glands when applied to the skin.

Another temporal relationship has been reported by Juel-Jensen (1972), who described four patients who repeatedly developed recurrent herpes simplex after smoking cannabis, to the degree that they had to give up use of the drug. Although very little is known about cannabis' effects on the skin, patients who have acne, recurrent herpes, or other skin problems and who smoke cannabis should be advised to observe a possible temporal relationship between smoking and worsening of their problem.

9. ALLERGIC MANIFESTATIONS

Periorbital edema is a well-known occurrence with acute cannabis intoxication (Ames, 1958). Both urticaria and angioneurotic edema have been reported with cannabis use. However, it is unclear whether these were due to true cannabis allergy or to contaminants in the cannabis preparations since patch tests and agar-gel diffusion studies using the patient's serum did not show true allergy in 10 subjects (Tennant *et al.*, 1971). These investigators felt that hashish tended to worsen symptoms, however, in patients who had a known allergy to pollens or house dust. This observation has been supported by Lewis and Slavin (1975) who had three atopic patients who developed asthma or rhinitis after smoking marihuana, despite the fact that all three had negative skin tests to marihuana. Shapiro *et al.* (1975) found that marihuana is antigenic and capable of eliciting an antibody response in the indirect Coombs test. It is interesting to note that some marihuana smokers with a positive antibody response also had abnormal liver function tests; hepatic dysfunction might explain the antibody response in some persons. Liskow *et al.* (1971) reported a patient with known allergy to ragweed who had an anaphylactoid response after smoking a marihuana cigarette for the first time. Scratch testing and passive transfer studies confirmed an immunologic basis for the response, indicating that some individuals may be significantly allergic to Δ^9-THC. Despite the paucity of reports available so far, it would appear clinically prudent to advise allergic patients that cannabis may worsen their symptoms.

10. PERIPHERAL NERVOUS SYSTEM TOXICITY

Dizziness and vertigo just following smoking have been reported by users (Halikas *et al.*, 1971), and auditory, vestibular, and peripheral nerve toxicity has been studied in chronic cannabis users (Spector, 1974; DiBenedetto *et al.*, 1977). Sophisticated testing showed vestibular function to be impaired but the detected deficit was of questionable clinical significance (Spector, 1974). Studies in a group of 27 male subjects administered cannabis for three weeks showed no deterioration in nerve conduction (DiBenedetto *et al.*, 1977). More peripheral neurologic defects were found among 44 Greek hashish users than among controls, but they consisted of a variety of types (Boulougouris *et al.*, 1976).

At this time there is no convincing evidence that cannabis causes any permanent neurologic impairment, and there is no explanation for the findings in the Greek field study, other than the possibility that some of the cases may have been alcoholic peripheral neuropathy.

11. HEMATOLOGICAL ABNORMALITIES

No significant hematologic abnormalities have been found consistently in clinical populations of cannabis users (Tennant *et al.*, 1971). Marihuana users in the Costa Rican field study had a lower mean hematocrit value and higher prothrombin time than did controls. This finding is difficult to evaluate since almost half of all subjects had intestinal parasites (Coggins *et al.*, 1976). Hematocrit value was slightly lowered in one closed-ward marihuana administration study (Jones *et al.*, 1976). The opposite effect was found in 30 Jamaican ganja smokers, most likely due to concomitant cigarette smoking which is known to produce polycythemia (Cruickshank, 1976). In Jamaica, ganja is customarily mixed with tobacco. At the present time there is no evidence to make one believe that cannabis consistently produces any hematologic disorder that can be measured by standard techniques.

12. RENAL-URINARY TOXICITY

To date, there have been no reports of renal toxicity except in cases of the cannabis injection syndrome (see Section 13). One case of urinary retention has been reported (Burton, 1979). In this case, a 55-year-old man ate cannabis butter and developed constipation and urinary retention which required urethral catheterization. Although the mechanism of action in this case is unknown, it may be due to interference with peripheral cholinergic activity. Cannabis is known to produce other anticholinergic effects such as dry mouth and constipation (Halikas *et al.*, 1971).

13. INJECTION SYNDROME

The most dramatic clinical toxicity is that seen following i.v. injection of aqueous extracts of cannabis plant products. Intravenous administration of marihuana may initiate a syndrome that was first reported by Henderson and Pugsley (1968) and later by King and Cowen (1969). Lundberg *et al.* (1971) found that most marihuana-related hospitalizations are due to injection. Characteristic early effects of i.v. injection of marihuana extracts include the rapid onset of nausea, vomiting, generalized pains, shaking chills, fever, tachycardia, and diarrhea. Within 12 hours, hypotension appears and is followed by a reversible renal insufficiency and possible rhabdomyolysis (Farber and Huertas, 1976). Initial

TABLE 4

Major Areas of Deficient Knowledge

Time and dosage requirements for acute and chronic toxic effects

Interactions of cannabis and tobacco on respiratory tract

Interactions of cannabis and alcohol on liver

Ability of cannabis to aggravate pre-existing cardiovascular, pulmonary, gastrointestinal, allergic, and dermatological diseases

Ability to cause cancer of lung

leukopenia is followed by a dramatic leukocytosis within the first 24 hours (Gary and Keylon, 1970). Early in the course of the syndrome, thrombocytopenia appears, which seems to be caused by a direct toxic effect of the injected extract.

The evidence is clear that cannabis extracts should not be injected i.v. since severe toxicity may occur.

✓ 14. MAJOR AREAS OF DEFICIENT KNOWLEDGE

The decade of the 1970s has witnessed a remarkable accumulation of knowledge on the clinical toxicity of cannabis. There still remains, however, considerable lack of knowledge. Table 4 lists some of the major areas of deficient knowledge.

The most needed information is that concerning the time-dose factor of cannabis toxicity. While considerable knowledge has been acquired about the time-dose relationship of clinical toxic effects with alcohol and nicotine, little is known about the dosage of cannabis and the duration of exposure required to produce toxic effects. This problem is particularly complex with cannabis since THC is fat-soluble and has a long serum half-life during the ß or elimination phase.

The interaction of cannabis with other drugs, particularly nicotine and alcohol, is poorly defined. Current evidence suggests that tobacco and cannabis when smoked concurrently produce more pulmonary damage than either smoked alone. Carcinogenic potential may therefore be enhanced by combined use. Liver dysfunction has frequently been observed in cannabis users and this may be due to a potentiation of the effects of alcohol brought about by simultaneous cannabis consumption.

Cannabis may have considerable ability to aggravate pre-existing disease. There is an increasing number of clinical reports which suggest that it can greatly complicate cardiovascular, pulmonary, gastrointestinal, hepatic, allergic, and dermatologic diseases.

Unfortunately, only long-term epidemiologic studies of humans will be able to confirm these relationships. That cannabis may lead to a higher incidence of lung cancer is of great concern.

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Cannabis, Marihuana, and Cannabinoid Toxicological Manifestations in Man and Animals

HARRIS ROSENKRANTZ, PhD

1. INTRODUCTION

The metamorphosis of cannabis usage from a sporadic religious, recreational, or medicinal event into a practice of consistent consumption has occurred in less than 50 years. Increased cannabis consumption in Western countries may in part be attributed to the emotional pressures generated by the dizzying strides of technological advancement concomitant with startling changes in societal values. The need to escape the problems of reality and project a passive confrontation against unacceptable restrictions of civilized society may play a role among the younger marihuana users. That marihuana became the drug of choice to facilitate a low-profile social revolt partially resulted from cheap accessibility and from the paucity of concrete scientific evidence about its cellular effects. Superimposed on these two factors was the incredible disagreement in the scientific community as to the potential health hazards or benefits of cannabis components.

In the U.S.A., the sound of alarm finally attained an intensity that stimulated governmental action in the late 1960s (U.S. Secretary HEW,

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1971). An additional factor favorable to research was the structural identification and synthesis of cannabinoids (Mechoulam, 1970). The burst of investigation that ensued culminated in hundreds of credible publications in which the less insidious effects of acute usage were differentiated from the more undesirable effects of prolonged consumption (Braude and Szara, 1976; Nahas, 1976; Waller *et al.*, 1976; Nahas and Paton, 1979). Despite the diverse explorations of the unique spectrum of pharmacologic expressions of cannabis, there is still no unified hypothesis of mechanism(s) of action for the cannabinoids. However, the mystery of molecular interference by cannabis constituents has not precluded documentation of an array of adverse effects. Nor has lack of understanding of the mode of action prevented investigation of possible beneficial applications (Bhargava, 1978; Cohen, 1980).

In order to assess more systematically the current knowledge of the toxicology of marihuana and pure cannabinoids, two historical periods of research have been arbitrarily distinguished, pre- and post-1970. This division is made because, in general, prior to 1968, various cannabis preparations (marihuana, hashish, ganja, charas, bhang, etc.) containing unknown proportions of Δ^9–tetrahydrocannabinol (Δ^9–THC) and other cannabinoids were studied in humans. Similarly, investigations in animals were conducted with crude cannabis extracts or partially purified Δ^9–THC. Moreover, no convenient analytical methodology was available to monitor circulating levels of cannabinoids. Finally, acceptable techniques for exposing animals to smoke had not been developed.

By 1970, a section of the National Institute of Mental Health (now known as the National Institute on Drug Abuse or NIDA) initiated a program that provided investigators with standardized marihuana cigarettes and pure cannabinoids (U.S. Secretary HEW, 1971; Waller, 1976). In subsequent years, methods were developed for determining blood and tissue levels of cannabinoids and their metabolites (Willette, 1976; Nahas and Paton, 1979; Jones, 1980).

Pre-1970 Observations in Man

Respiratory distress and lethality associated with exposure to hemp dust foreshadowed the potential health hazard of cannabis to man as early as 1859 (Croudace, 1859; Deakin, 1880; Walker, 1896; Bouhuys *et al.*, 1969). Although cannabinoid-induced lethality in man has been difficult to establish, cannabis-related deaths have been reported (Heyndrickx *et al.*, 1969; Özen and Sözen, 1969; Nahas, 1971).

Between 1848 and 1971, descriptions of approximately 51 cases of cannabis poisoning involving nine countries appeared in the medical literature (Waller *et al.*, 1976; Kalant *et al.*, 1983). Symptoms and signs of anisocoria, aphonia, catalepsy, tremors, cardiac and renal dysfunction or coma were observed. Cannabis preparations included crude marihuana extracts, ganja, marihuana, hashish, and Δ^9–THC administered by inhalation, i.v., or orally. As would be expected, the type of symptom, intensity, and duration of effects were related to cannabinoid dosage and route of administration. This interrelationship may explain why identical toxic symptoms were not seen in all cases of cannabis poisoning. Inhaled low doses of marihuana evoked euphoria while large inhaled or oral doses of Δ^9–THC elicited fright, panic, and hallucinogenic-like encounters (Brill *et al.*, 1970; Hollister, 1971a and b; Hochman and Brill, 1971).

The behavioral aberrations evoked by inhalation of marihuana or hashish smoke in man were vividly described by 19th century experimenters. The spectrum of personality alterations encompassed euphoria, uninhibited laughter, lassitude, perceptual anomalies, disarray of thoughts, and depersonalization. These same manifestations were observed by pre-drug-culture researchers as well as by recent investigators. With increasing doses of marihuana, the sensory disturbances of mild intoxication escalated to hysteria and toxic psychoses (Bromberg, 1934, 1968; Adams, 1942; Mayor's Committee, 1944; Chopra and Chopra, 1957; Allentuck and Bowman, 1966; Keeler, 1967; Talbott and Teague, 1969). Responses to ganja and hashish were similar (Fraser, 1949; Grossman, 1969). Allowing for the differences in the latency of onset of effects related to route of administration, similar behavioral anomalies were also seen for orally administered (Ames, 1958; Clark and Nakashima, 1968; Melges *et al.*, 1970) or i.v. injected (Gary and Keylon, 1970) cannabis preparations. That many of the behavioral effects of cannabis could be attributed to Δ^9–THC was elegantly demonstrated by Isbell *et al.* (1967) and Hollister (1971a). The biphasic nature of marihuana action in man, initial CNS-stimulation (heightened perceptions) followed in time by CNS-inhibition (sedation), was subsequently confirmed in animal models.

The early reports of toxicological signs of marihuana consistently included tachycardia, reddening of the conjunctivae, and elevated pulse rate (Chopra, 1969; Hollister, 1971b). Subjective complaints of tremors and ataxia (Mayor's Committee, 1944; Smith, 1968; Weil *et al.*, 1968; Brill *et al.*, 1970) were accompanied by clearly visible signs in cases of severe intoxication (King and Cowen, 1969). Isolated reports of neurotoxicity (Munch, 1968), EEG alterations (Wikler and Lloyd, 1945; Hollister, 1971a; Rodin and Domino, 1970), liver and renal dysfunction (Kew *et al.*, 1969; King and Cowen, 1969), and blood changes (King *et al.*, 1970; Hollister, 1971b) appeared. Inability to compare effects of Δ^9–THC (or other cannabinoids) at equivalent dosages contributed to disparities. Variability of dosage and of routes of administration also prevented the demonstration of tolerance and physical dependence (Williams *et al.*, 1946; West, 1955; Brill *et al.*, 1970).

Superimposed on the difficulties of varied formulations and doses of cannabis components were the uncontrolled aspects of the extent and duration of experience with cannabis and polydrug use among subjects studied. All these factors made it necessary to develop standardized cannabis preparations and more rigorous guidelines for selection of volunteers. Before extensive human testing under more rigidly controlled conditions could be exercised, risk assessment of the cannabis products had to be performed in appropriate animal paradigms.

Pre-1970 Observations in Animals

Because of the overlap in time during which natural and synthetically produced Δ^9–THC were used, the review of pre-1970 observations will deal mainly with studies utilizing crude cannabis preparations. Investigations using natural or synthetic cannabinoids before 1970 will be discussed below in the section on more recent findings.

The classical work of Walton *et al.* (1938) provided data on isolation procedures, estimates of potency by means of the dog ataxia bioassay and rabbit corneal anesthesia (areflexia) test, and acute toxicity. Interestingly enough, the source material consisted of hemp plants grown in Mississippi under conditions similar to those established in later years for the NIDA marihuana program. Administration of purified "red oil" concentrates revealed the effect of route of administration. Subcutaneous or percutaneous administration required approximately 50 times the i.v. dose but the biological responses were more prolonged. Potency by the oral route was approximately one-sixth that of the i.v. route, a ratio in agreement with Δ^9–THC findings in man (Isbell *et al.*, 1967). Fatal acute i.v. doses of the concentrate for dogs ranged between 125–350 mg/kg and cardiac failure associated with cerebral hyperemia and pulmonary edema occurred in 0.5–24 hr. This finding is in remarkable agreement with the data on acute toxicity of illicit hashish oil in monkeys (Rosenkrantz *et al.*, 1981).

Other early investigators using crude cannabis or marihuana extracts reported inhibition of rat brain respiration (Bose *et al.*, 1963a), decreased canine respiratory excursions (Bose *et al.*, 1963b), and the biphasic behavioral response of initial excitement followed by depression in dogs (Bose *et al.*, 1964b). Carlini and coworkers observed disrupted maze-solving ability (Carlini and Kramer, 1965), tolerance development to disturbed performance on some tasks (Carlini, 1968), and stimulation of aggression (Carlini and Masur, 1969) in rats. Hashish initiated hypothermia in mice, prolonged barbiturate sleep time, and depressed spontaneous activity in rodents (Garattini, 1965; Dagirmanjian and Boyd, 1962). Synthetic derivatives and natural cannabinoids inhibited respiration in mice and dogs (Loewe, 1946) and anesthetized cats (Dagirmanjian and Boyd, 1962), impaired rat operant behavior (Boyd *et al.*, 1963), and elicited aberrant EEG patterns in cats, rabbits and rats (Bose *et al.*, 1964a; Lipparini *et al.*, 1969). Cannabis or THC also inhibited polysynaptic reflexes in cats and the linguomandibular reflex in dogs (Dagirmanjian and Boyd, 1962; Sampaio *et al.*, 1967). In general, the early researchers were observing CNS-inhibitory effects.

2. EXPERIMENTAL TOXICOLOGY

When interpreting the adverse effects of marihuana and pure cannabinoids, one should consider dosage, route of administration, type of drug formulation, generation of active metabolites, rate of metabolic degradation, rapidity of drug and metabolite excretion, and duration of treatment. Intertwined among these variables is variation in the rate of tolerance development to diverse physiological processess affected by cannabis constituents (see Jones, this volume).

In the design of appropriate animal paradigms for assessing risk potential of marihuana or cannabinoid use, differences in bioavailability, physiological and morphological responses, and drug metabolism between man and animal are of paramount consideration. For example, whereas man prefers to inhale marihuana, this process cannot be exactly duplicated in any animal model. Furthermore, in the strategy of utilizing large numbers of animals in order to achieve statistically meaningful data, often a species is chosen (e.g., rat) in which the metabolic pathways are dissimilar to those of man. Another aspect of investigation that is usually criticized by proponents of marihuana usage relates to the "excessive doses" administered to animals. Few ears and minds are receptive to the concept that large doses must be used in order to evoke toxic signs deliberately. It is a necessary procedure in risk assessment to induce drug responses with large doses so that acute poisoning or delayed or cumulative toxicity at relevant doses can more easily be recognized.

It is my main intention to review those investigations of experimental toxicology in which standardized marihuana cigarettes and pure cannabinoids were used. Under such circumstances, comparisons of drug-induced anomalies in man and animals are more reasonable. In addition, some emphasis will be placed on chronic studies since the effects of prolonged treatment may be more pertinent for the assessment of cannabis as a health hazard in man.

Cannabis Preparations

Among the 421 compounds thus far identified in cannabis are approximately 61 with cannabinoid structures (Turner *et al.*, 1980). Depending on the geographical origin of the plant, the content of individual cannabinoids varies widely (Small and Beckstand, 1973; Holley *et al.*, 1975). The content of Δ^9–THC steadily decreases at a rate of approximately 5% per year in plant material stored at low temperatures (Turner *et al.*, 1973). Although several of the cannabinoids are known to have biological effects, only structures closely related to Δ^9–THC elicit euphoria at low doses (Grunfeld and Edery, 1969; Perez-Reyes *et al.*, 1973b; Hollister, 1974). For example, decarboxylation of tetrahydrocannabinolic acid to Δ^9–THC must occur before expression of its psychoactive effect is observed (Yamauchi *et al.*, 1967; Claussen and Korte, 1968; Shoyama *et al.*, 1969; De Zeeuw *et al.*, 1972; Tampier and Linetzky, 1973; Kinzer *et al.*, 1974).

Marihuana Cigarettes

In general, most controlled investigations of marihuana in human volunteers and experimental animals in the United States have been performed with cannabis grown at the University of Mississippi (Waller, 1976). The NIDA marihuana and cannabinoid-extracted cigarettes were fabricated from this material by a contractor.

In order to define more completely the NIDA reference marihuana cigarette, several physical and chemical parameters should be considered. The consistency of the cigarettes has been assessed by measurement of mass, total particulate matter, burning time and temperature, residual butt length, the concentration of carbon monoxide generated, and the smoke particle size (Huber *et al.*, 1979; Rosenkrantz and Fleischman, 1979). The weight of marihuana cigarettes has predominantly been between 0.85 and 1.05 g irrespective of cannabinoid content. The length of the cigarettes has been 84–85 mm. Generally, eight puffs per cigarette have been achieved with a volume of 40–50 ml/puff. Residual butt lengths have been 15–25 mm. The cigarette burning rate, which is dependent on tightness of packing and mass, has been between 8 and 9 mm/min. Of crucial importance from a toxicological viewpoint is the total particulate matter produced on combustion. This parameter relates to cigarette weight, since the larger the mass the greater the quantity of particulates. In addition, the content of cannabinoids contributes to the weight of particulates. The total particulate matter from eight puffs of a single 1 g marihuana cigarette (obtained on a Cambridge filter under standard smoking conditions) has varied from 35 to 40 mg. Under these same conditions, approximately 0.4% carbon monoxide has been generated.

Because of the variability of marihuana cigarettes, it seems clear that proper selection of cigarettes from the same batch of marihuana should be exercised for each study being anticipated. The factor of variable air resistance during generation of a puff should also be considered. It has not been uncommon to find different lengths and thicknesses of marihuana cuttings that have favored or impeded airflow through the cigarettes (Fehr and Kalant, 1972; Rosenkrantz and Braude, 1974).

Another aspect of marihuana or hashish combustion concerns pyrolytic destruction or interconversion of cannabinoids at burning temperatures. Such transformations are in part temperature-dependent and at the usual burning temperature of approximately 600°C, little or no interconversion of cannabinoids has been seen (Shoyama *et al.*, 1969; Agurell and Leander, 1971; Coutselinis and Miras, 1971; Mikeš and Waser, 1971; Waser *et al.*, 1971). Approximately 50% of Δ^9–THC survives combustion and pyrolytic losses as well as losses due to butt entrapment; this fact should be considered in dosage selection (Miras *et al.*, 1964; Fehr and Kalant, 1972; Manno *et al.*, 1970; Rosenkrantz *et al.*, 1974). There is some question whether CBD can be converted to Δ^9–THC during pyrolysis (Quarles *et al.*, 1973; Kephalas *et al.*, 1976; Salemink, 1976; Spronck *et al.*, 1978). A complex profile of marihuana smoke constituents has been reported by Novotny *et al.* (1976).

Cannabinoids

The production of adequate supplies of pure cannabinoids has essentially been via organic synthesis (Petrzilka, 1971; Mechoulam *et al.*, 1972; Razdan *et al.*, 1974; Turner, 1980). The purities of Δ^9–THC (96%), Δ^8–THC (98%), cannabidiol (CBD, 99% as oil or crystalline product), cannabichromene (CBCh, 95%), and cannabinol (CBN, 97%) were established by gas and thin-layer chromatography before NIDA shipments were made to investigators. Various radiolabeled cannabinoids (and their metabolites) necessary to elucidate pharmacokinetics and metabolic pathways have also been synthesized (Wall, 1971; Pitt *et al.*, 1972; Agurell *et al.*, 1973; Burstein, 1973; Mechoulam *et al.*, 1976). The stability of Δ^9–THC has been studied under various conditions of temperature and pH (Garrett and Tsau, 1974).

NIDA has also arranged for the production of a crude marihuana extract (Δ^9–THC content approximately 20%) as a reference material (Thompson *et al.*, 1973a). Intercepted illicit preparations of hashish oil with Δ^9–THC content between 10% and 30% have been investigated for toxicity (Rosenkrantz *et al.*, 1981).

Drug Formulation

The diversity of drug formulations of pure cannabinoids as well as crude marihuana or hashish extracts has somewhat complicated interlaboratory comparison of pharmacological and toxicological findings. In a random sampling of 80 published papers, less than 20% described the details of drug formulation. Most often the final concentration of cannabinoid was lacking and an estimate of administered volumes of preparation could not be calculated.

Although little concern may be exercised in single-dose studies, the vehicle(s) in drug formulations may exert inherent toxicity when given repetitively. Even in acute experiments, the use of a psychoactive vehicle such as ethanol may be questionable. On the other hand, some compromise is necessary in toxicological studies because a solvent or dispersant must be used in order to achieve the large dosages required. The water-insoluble nature of the cannabinoids restricts the selection of diluents (Rosenkrantz *et al.*, 1972).

Pure Cannabinoids and Marihuana Extracts

The types of vehicles utilized to prepare cannabis formulations have provided suspensions, emulsions, and true solutions. In the selection of a formulation, route of administration should be considered since even aqueous emulsions may induce embolism after i.v. introduction. Selection of a dispersant has been based on a compromise of various factors including route of administration. Some of these factors are the desired concentration of cannabinoid, tolerable concentration of organic dispersant, physical state and stability of the formulation, frequency of administration of the preparation, duration of treatment and species sensitivity to the vehicle (Rosenkrantz *et al.*, 1972). The types of vehicles have ranged from organic solvents (e.g., ethanol, glycols, acetone, dimethylsulfoxide) to natural materials such as glycerol, vegetable oils and serum proteins. In many instances, polysorbate 80 (Tween 80) has been used as an emulsifier. Solubilization of Δ^9-THC and cannabis extracts has been achieved in polyethyoxylated vegetable oil (Cradock *et al.*, 1973), Arlacel-Tween (Moreton and Davis, 1972) and Emulphor (Olsen *et al.*, 1973). The variability in time and duration of response due to different vehicles has been examined (Fernandes and Coper, 1971; Rosenkrantz *et al.*, 1972; Sofia *et al.*, 1974).

By and large, aqueous systems desirable for parenteral administration are of limited use for toxicological studies since cannabinoid concentrations attainable are usually less than 1%. A dilutable aqueous emulsion containing 4% Δ^9–THC has been formulated in 12% sesame oil and 1% polysorbate 80 (Rosenkrantz *et al.*, 1974). This cannabinoid formulation has been suitable for administration by any parenteral route and orally. To achieve the large doses necessary to evoke maximum toxic manifestations acutely or chronically by the oral route, sesame oil readily permits solubilization of cannabinoids or cannabis extracts to concentrations of 400 mg/ml (Thompson *et al.*, 1974; Rosenkrantz *et al.*, 1975). An aerosol preparation of Δ^9–THC has also been produced (Olsen *et al.*, 1976).

Marihuana and Placebo Cigarettes

In North American studies, standard marihuana and cannabinoid-extracted marihuana (placebo) cigarettes have generally been supplied by NIDA. The Δ^9–THC content of marihuana cigarettes manufactured from different harvests has varied from approximately 0.9% to 2.8% (Rosenkrantz, 1979; Rosenkrantz and Fleischman, 1979). The marihuana cigarettes have been devoid of Δ^8–THC and have contained less than 0.2% of each of the other major cannabinoids. Cannabinoid-extracted marihuana had less than 0.001% Δ^9–THC, no Δ^8–THC, and less than 0.008% of each other major cannabinoid. At a storage temperature of 5°C, Δ^9–THC in NIDA marihuana cigarettes decomposed at a rate of approximately 2.5% per year.

For the determination of inhalation lethality, placebo or marihuana cigarettes have been impregnated with pure cannabinoid (Rosenkrantz *et al.*, 1974; Rosenkrantz and Hayden, 1979). With such "spiked" marihuana cigarettes, it has been possible to differentiate cannabinoid-induced mortality from death due to carbon monoxide poisoning.

Treatment Protocols

Variations in the onset of action, intensity of response, and duration of effect can usually be attributed to a combination of factors such as dose, formulation vehicle, and route of administration as well as species and sex differences of sensitivity. Often a response is no longer visible after repeated administrations because of development of metabolic or functional tolerance. Interlaboratory comparisons of measured parameters should be made at equivalent times after drug administration, and at comparable frequencies of observation. For example, the biphasic response of animals to cannabis preparations may appear inverted at higher dosages since CNS-inhibition will be more apparent than CNS-stimulation in the early stage of response. The duration of treatment is also important since effects seen after 14 days of administration may be quite different from those observed at 90 days. Many of the disparities occurring in the area of behavioral responses, hormone alterations, immune impairment, morphological changes, and teratology might be attributable to differences in the treatment protocols used in various cannabis investigations.

Duration of Treatment

In the assessment of findings initiated by cannabis preparations, an adequate distinction must be made between short- and long-term treatment. Too often, opposite effects described in conflicting reports can be traced to a difference in the duration of treatment. Even in the instance of pharmacokinetic studies, radiolabeled tracers have been administered as a single acute dose or at some time after short-term administration of a nontracer cannabinoid. Martin *et al.* (1974) studied 9-nor-cannabinoids, thus precluding conversion of the THC analog to its active hydroxylated metabolite.

It seems reasonable to consider a single or repeated treatment in one day as an acute study, treatments over 2 to 14 days as subacute studies, and administrations over 30–90 days as a subchronic study. Long-term treatments are those which extend beyond 90 days. Under such definition of duration of treatment, disappearance, appearance or reversal of aberrations can be related to changes in bioavailability of the drug, biphasicity of responses, stimulation of metabolism, activity of metabolites, tissue storage of drug, and the development of functional tolerance.

Duration of treatment should also be related to the duration of response. Behavioral effects in pigeons persist for days (McMillan, 1977). The CNS-inhibition observed in acute studies in rats did not permit the prediction of hyperactivity, fighting aggression, tremors, and clonic convulsions observed during prolonged treatment with Δ^9–THC (Thompson *et al.*, 1973a and b).

Route of Administration

As early as 1937, Walton *et al.* (1938) astutely described variations in responses evoked by cannabis extracts in dogs, in relation to different routes of administration. Percutaneous and s.c. applications required large doses to elicit effects and produced delayed and prolonged responses. Intravenous or intracisternal injections of lower doses elicited prompt effects of short duration. Administration by the oral route gave effects somewhere in between. Similar findings were obtained in rabbits.

The influence of route of administration on cannabinoid action was also seen in other species and was in conformity with the findings of Walton *et al.* (1938). The i.p. route was more effective than the s.c.

route in monkeys (Grunfeld and Edery, 1969). To elicit equivalent behavioral effects in rodents, dosages of Δ^9–THC had to be increased dramatically as the route was changed from i.v. to i.p. to oral (Forney and Kiplinger, 1971; Sofia *et al.*, 1974). Using tritiated Δ^9–THC, Ho *et al.* (1971b) demonstrated that Δ^9–THC remained in the abdominal cavity after i.p. injection. This would explain the delay of onset and attenuated response. As would be expected, ^{14}C–Δ^9–THC was retained longer in rat lungs after smoke inhalation than by i.v. injection (Leighty, 1973). However, the reverse was true for disposition of Δ^9–THC in rat brain.

Criticism of the use of nonpulmonary routes for administration of cannabinoids cannot be justified since these routes yield results similar to those observed after inhalation and offer the advantages of more convenient repetitive dosing as well as a wider selection of dosages. Sufficient documentation of qualitatively similar toxic signs evoked by inhalation of marihuana smoke and by orally administered Δ^9–THC exists for humans and animals (Hosko *et at.*, 1973; Perez-Reyes *et al.*, 1973a; Rosenkrantz and Braude, 1976). Indeed, in more rigidly controlled experiments using rodents, comparable immunological impairment (Rosenkrantz, 1976), embryotoxicity (Rosenkrantz, 1979), hormone derangements (Rosenkrantz and Esber, 1980), and morphologic alterations of lungs (Rosenkrantz and Fleischman, 1979) were observed by inhalation and oral treatments with cannabinoids. Cannabinoid responses seen after i.v. administration have also validated oral findings (Perez-Reyes *et al.*, 1973b; Thompson *et al.*, 1974). The nearly identical LD_{50}s obtained by inhalation and i.v. established the validity of comparison of marihuana-evoked responses to those arising from cannabinoid injection (Rosenkrantz *et al.*, 1974).

Dosages

The selection of doses for assessing the pharmacological effects of cannabis constituents has depended on the specific biological objective. With the emergence of high potency marihuana, hashish oil, and synthetic Δ^9–THC, the usual dose used to achieve a "high," formerly 0.05 mg/kg, has virtually more than tripled in recent years. That is not to say that a larger dose of Δ^9–THC is needed to experience a "high," but rather to focus attention on the higher dosages currently being consumed by man. The probability of encountering cannabis toxicity has become more real.

In order to compare toxicological effects of complex marihuana or hashish smoke with those of pure cannabinoids, it seems reasonable to relate dosage of the former to the content of cannabinoids in the cannabis preparation used. Although several cannabinoids have biological effects, the euphoric response is principally accounted for by Δ^9–THC when cannabis is given at small doses (Edery *et al.*, 1971). Therefore, Δ^9–THC doses in marihuana have been used as a reference point in toxicity studies. In general, except for pyrolytic losses, Δ^9–THC is not significantly transformed to other cannabinoids during combustion (Rosenkrantz and Braude, 1974). The question of metabolite contribution to biological activity of Δ^9–THC has in part been answered (Lemberger *et al.*, 1976; Wilson and May, 1976). The combination of Δ^9–THC and 11–OH–Δ^9–THC provides the spectrum of pharmacological action previously attributed to Δ^9–THC alone (Paton, 1975).

Cannabinoids and Extracts

In pharmacological investigations in animals, doses of Δ^9–THC have ranged from approximately 0.5–10 mg/kg irrespective of route of administration. Acute and chronic toxicity experiments have incorporated nonlethal doses between 10 and 500 mg/kg for the oral route (Thompson *et al.*, 1973a and b, 1974; Huy *et al.*, 1975b; Rosenkrantz *et al.*, 1975), 5 and 45 mg/kg for the i.v. route (Thompson *et al.*, 1974), and 3 and 150 mg/kg by the s.c. route (Thompson *et al.*, 1975; Banerjee *et al.*, 1976).

Cannabis extracts have been used at dosages related to their Δ^9–THC content (Thompson *et al.*, 1973a; Carlini *et al.*, 1974; Gupta *et al.*, 1974; Lukas and Temple, 1974). In effect, doses of crude extracts as large as 1,500 mg/kg were administered daily.

Marihuana

For reasons explained above, the Δ^9–THC content has been utilized as the reference point for marihuana or hashish potency. In addition, Δ^9–THC has been studied more extensively than other cannabis constituents. Therefore dose-response investigations in man and animals have usually been based on the Δ^9–THC content even though the drug being tested was marihuana or hashish.[1]

With respect to the NIDA marihuana cigarette, it has already been mentioned that the Δ^9–THC content has varied from 0.9%–2.8%. By varying the number of puffs and the number of simultaneously smoked cigarettes, the Δ^9–THC dose can be manipulated. In this manner, Δ^9–THC doses between 0.05 and 5 mg/kg have been achieved in animal and human studies (Carlini *et al.*, 1974; Rosenkrantz and Braude, 1974; Cohen, 1976; Mendelson *et al.*, 1976; Fleischman *et al.*, 1979; Rosenkrantz, 1979). Where a larger content of Δ^9–THC in marihuana is desirable, techniques for impregnating plant material with Δ^9–THC can be used (Rosenkrantz and Braude, 1974; Lewis and Turner, 1978).

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[1] Editors' footnote: Several groups have reported that certain effects of a specified dose of cannabis are greater than those of the contained dose of pure THC (see, for example, Karniol and Carlini, 1972; Carlini *et al.*, 1974; Fairbairn and Pickens, 1981).

Doses Relevant to Man

The caution expressed endlessly about extrapolating responses in animals to predict those in man frequently causes observers to ignore the importance of adverse effects observed in nonhuman species (Jones, 1980). The additional confounding variables such as alternative routes of administration and differences in dosage contribute further to an obscuring of the conclusions. Nevertheless, a posture must be assumed if animal paradigms are to be at all acceptable.

Although by no means the only approach for estimating the relevance of animal doses to man, the application of dose based on body surface area has aided in the interpretation of human and animal responses to cannabis products (Rosenkrantz, 1976). That such an approach was more than reasonable has been substantiated by the finding of similar levels of circulating Δ^9–THC in man and animals when equivalence of doses is calculated on this basis (Rosenkrantz, 1979; Rosenkrantz and Fleischman, 1979). A summary of estimated relevant doses for several species is given in Table 1. Despite lack of specific agreement as to the definition of moderate or heavy use, a consensus has emerged whereby the consumption of 1, 3, or 6 marihuana cigarettes per day is considered as light, moderate, or heavy use respectively (Dornbush *et al.*, 1976). Indeed, in controlled human studies in hospital settings, as many as 20 marihuana cigarettes were enjoyed by some subjects in a day (Mendelson *et al.*, 1976).

The data in Table 1 provide estimates of relevant doses by two routes of administration. Such data may be useful in risk assessment as well as in the interpretation of discrepancies between findings in man and animals. Furthermore, the data may reveal differences in species susceptibility if a relevant dose initiates a biologic effect in one species and not in another. In man, plasma levels of Δ^9–THC have generally been between 20 and 200 ng/ml and with relevant doses in animals, calculated on the basis of body surface area circulating levels of Δ^9–THC have ranged from 25 to 300 ng/ml (Rosenkrantz and Fleischman, 1979). It is not unrealistic to assume that animal doses are relevant to those used by man when drug levels in blood are similar for both.

LD_{50} Values

The remarkable difference in inhalation or i.v. LD_{50} values from

TABLE 1

Equivalent Δ^9–Tetrahydrocannabinol Doses in Man and Animals Based on Body Surface Area[a]

Route and Usage	mg/kg Δ^9–THC (marihuana, 1% THC; hashish, 5% THC)					
	man[c]	monkey	dog	rabbit	rat	mouse
Inhalation[b], light	0.1–0.5 (1 cig/day)	0.3–1.5	0.2–1	0.4–2	0.7–4	1–6
moderate	0.3–1.5 (3 cig/day)	0.9–4.5	0.6–3	1.2–6	2–10	4–18
heavy	0.6–3.0 (6 cig/day)	1.8–9.0	1.2–6	2.4–12	4–20	7–36
Approximate LD_{50} (inhalation)		125[d]	> 60[d]	55	40	45
Oral[e] light	0.3–1.5 (1 cig equiv.)	1–5	0.6–3	1.2–6	2–10	4–18
moderate	0.9–4.5 (3 cig equiv.)	3–14	2–9	4–18	6–30	10–54
heavy	1.8–9.0 (6 cig equiv.)	5–27	4–18	12–36	12–63	20–100
Approximate LD_{50} (oral)		15,000[f]	> 10,000[f]	> 5,000[f]	1,000	2,000

a. Dose based on body surface area: conversion factors are approximately 3, 2, 4, 7, and 12 for monkey, dog, rabbit, rat, and mouse, respectively.

b. Assumes a 50% loss of Δ^9–THC due to combustion and butt entrapment.

c. Assumes 50 kg mean body weight to include younger users.

d. Nearly i.v. LD_{50} dose; inhalation and i.v. LD_{50} values shown to be the same for rat.

e. Oral route required at least 3x the inhalation dose.

f. Estimates based on morbidity and not deaths.

those obtained by the oral route suggests a greater cannabinoid risk when marihuana is inhaled than when it is ingested orally. Although LD_{50}s vary among species and are affected by the formulation vehicle, meaningful values have been confirmed by various investigators (Table 2). Incorporating allowances for different species and drug formulations, safety estimates of investigative doses of Δ^9–THC can be achieved by reference to the LD_{50} values. The doses utilized in a study can also be compared with the ranges of proposed doses given in Table 1 to ascertain relevance to human consumption.

For rodents, representative LD_{50} ranges are: i.v., 30 to 60 mg/kg; i.p., 400 to 600 mg/kg; and orally, 800 to 1,600 mg/kg. The i.p. LD_{50} for bat was 535 mg/kg (Brown *et al.*, 1974) and the i.v. LD_{50} for rabbit was 60 mg/kg (Cradock *et al.*, 1973). The i.v. LD_{50}s for Δ^8–THC and its 11-substituted derivatives in mice were approximately 30 to 100 mg/kg (Watanabe *et al.*, 1980). In oral studies, female rodents were more sensitive to Δ^9–THC than males (Thompson *et al.*, 1973b). In general, mean lethal doses of Δ^8–THC in rats, dogs and monkeys were similar to those of Δ^9–THC (Thompson *et al.*, 1973b). Multiple housing of animals may influence LD_{50} values (Sofia, 1972a). Some species are more sensitive to polysorbate 80 than to other vehicles and the use of this vehicle may distort lethality measurements (Rosenkrantz *et al.*, 1972; Mantilla-Plata and Harbison, 1974; Rosenkrantz *et al.*, 1974). CBCh pretreatment has been reported to reduce the LD_{50} of Δ^9–THC (Hatoum *et al.*, 1980).

Of interest is the distinction between the LD_{50}s for rodents and those for monkeys and dogs (Table 2). Clearly Δ^9–THC was less lethal in higher mammals when given by both the i.v. and oral routes. In addition, whereas the oral:i.v. lethal dose ratio was approximately 20 for rodents, it was nearer 100 for monkeys. This factor must also be considered in determining whether an experimental dose is relevant to man.

It has been found that cannabinoids given in marihuana extracts are less lethal than the same doses of pure cannabinoids. The i.v. LD_{50}s for pure Δ^9–THC, CBD and CBCh in monkeys were 128, 212, and 270 mg/kg, respectively (Thompson *et al.*, 1974; Rosenkrantz *et al.*, 1981). CBCh in mice yielded a value of 113 mg/kg for the i.p. route and more than 3,000 mg/kg for the oral or s.c. routes (Hatoum *et al.*, 1980). Crude marihuana extract with approximately 20% Δ^9–THC (and less than 2% each of CBD and CBCh) had an i.v. LD_{50} of 381 mg/kg in monkeys. Similar LD_{50} values were obtained for illicit hashish oil: 435 mg/kg for hashish oil containing approximately 31% Δ^9–THC, 10% CBD, 3% CBCh, and 3% CBN and 326 mg/kg for hashish oil containing approxi-

TABLE 2

Δ^9–*Tetrahydrocannabinol-Evoked Mortality after a Single Treatment by Different Routes in Various Species*

Species	Route Admin.	Treatment Vehicle	LD_{50}[a] (mg/kg)	Reference
Monkey, rhesus	i.v.	13% sesame oil + 1% Tween 80	128	Thompson *et al.*, 1974
rhesus	oral	sesame oil	> 1-2,000	Thompson *et al.*, 1974
Dog, mongrel	i.v.	acetone	100[b]	Walton *et al.*, 1938
mongrel	i.v.	5% serum albumin	> 24	Dewey *et al.*, 1972b
beagle	i.v.	ethanol	> 40	Rosenkrantz *et al.*, unpublished data
Rat, Holtzman	i.v.	10% Tween 80	29[c]	Phillips *et al.*, 1971
Fischer	i.v.	7% sesame oil + 0.5% Tween 80	40	Rosenkrantz *et al.*, 1974
Sprague-Dawley	i.v.	5% serum albumin	100	Dewey *et al.*, 1972a
Holtzman	i.p.	10% Tween 80	372[c]	Phillips *et al.*, 1971
Fischer	i.p.	7% sesame oil + 0.5% Tween 80	670	Rosenkrantz *et al.*, 1974
Sprague-Dawley	i.p.	5% serum albumin	430	Dewey *et al.*, 1972a
Holtzman	oral	10% Tween 80	666[c]	Phillips *et al.*, 1971
Fischer	oral	13% sesame oil + 1% Tween 80	800	Rosenkrantz *et al.*, 1974
Sprague-Dawley	oral	5% serum albumin	> 2,000	Dewey *et al.*, 1972a
Wistar-Lewis	oral	97% sesame oil + 3% ethanol	1,160	Thompson *et al.*, 1973b
Fischer	oral	sesame oil	1,015	Thompson *et al.*, 1973b
Fischer	oral	sesame oil	1,270	Rosenkrantz *et al.*, 1974

Mouse, albino Cox	i.v.	10% Tween 80	43[c]	Phillips *et al.*, 1971
Swiss-Webster	i.v.	5% serum albumin	60	Dewey *et al.*, 1972a
albino Cox	i.p.	10% Tween 80	454[c]	Phillips *et al.*, 1971
Swiss-Webster	i.p.	5% serum albumin	168	Dewey *et al.*, 1972a
Swiss	i.p.	10% glycol + 1% Tween 80	270	Sofia, 1972
ICR	i.p.		276	Hatoum *et al.*, 1980
albino Cox	oral	10% Tween 80	482[c]	Phillips *et al.*, 1971
Swiss-Webster	oral	5% serum albumin	1,900	Dewey *et al.*, 1972a
Swiss CD-1	oral	sesame oil	2,000	Rosenkrantz *et al.*, unpublished data

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a. Predominantly male animals were used
b. Estimate of 80% Δ^9–THC in 'red oil'
c. Natural Δ^9–THC

mately 12% Δ^9–THC, 5% CBD, 2% CBCh, and 6% CBN (Rosenkrantz *et al.*, 1981).

Irrespective of route of administration, lethal doses cause apnea and cardiac arrest. When the apnea is successfully treated in monkeys and rats, cardiac failure is the cause of death.

3. NEUROTOXICITY

The stimulation of higher centers in the CNS was evident from man's first encounter with cannabis. The bimodal response to marihuana, hashish, or Δ^9–THC (described below) expanded the possibilities of pharmacological effects and toxicological manifestations. Despite the inability to document euphoria in animal models, non-targeted staring into space, observed in monkeys, suggests the psychoactivity of cannabis components.

Perhaps the most characteristic responses to small and large doses of drug are, respectively, mild behavioral aberrations and signs of gross neurotoxicity, manifested by tremors and convulsions. In those instances in which small doses were administered, prolongation of treatment permitted the subsequent emergence of behavioral neurotoxicity (Rosenkrantz *et al.*, 1975; Luthra *et al.*, 1976). Similar toxic signs were seen in rodents when cannabis formulations were given by either the inhalation or the oral routes in both acute and chronic studies.

Behavioral Aberrations

Behavioral profiles of experimental animals exposed to marihuana or Δ^9–THC visibly confirm the biphasic response of CNS-stimulation and CNS-inhibition. With large doses, depression is sustained until tolerance develops. At lower doses, hyperactivity and hypersensitivity (particularly to auditory or tactile stimuli) are evident, but with continued treatment tolerance also develops toward CNS-stimulation (Luthra *et al.*, 1976; Rosenkrantz and Braude, 1976). That tolerance occurs in both man and animals can no longer be disputed (Dewey *et al.*, 1976b; Hollister, 1979; see also Jones, this volume).

Motor Activity after Acute Treatment

A dose-related effect on motor activity has been observed in many species after the administration of marihuana or pure cannabinoids. In man, the common symptoms encompass euphoria and heightened sensory perceptions during the initial phase of CNS-stimulation (Hollister, 1971b; Dornbush *et al.*, 1976; Fried, 1977; Jones, 1980). Lethargy and sedation are prominent features in the second phase although loss of coordination can also be measured. Environmental and psychosocial factors are known to enhance or attenuate human responses.

Assessment of motor activity in experimental animals has been accomplished more readily, and at reasonable Δ^9–THC doses of 0.1 to 50 mg/kg given parenterally or 50 to 3,000 mg/kg orally (Table 3). A single treatment with relevant doses initiated transient hyperactivity followed by lethargy and sedation in monkeys (Scheckel *et al.*, 1968; Grunfeld and Edery, 1969). Massive oral doses in the same species elicited similar but more severe and longer-lasting depression (Thompson *et al.*, 1973b). In the dog and cat, a stuporous state or ataxia predominated (Grunfeld and Edery, 1969; Dewey *et al.*, 1970; Kaymakçalan and Deneau, 1971; Oskoui, 1971) which was enhanced by large oral doses (Thompson *et al.*, 1973b).

Spontaneous activity or simple motor tasks were generally inhibited in rodents. Single parenteral Δ^9–THC doses of 1 to 20 mg/kg in rats decreased motor activity (Henriksson and Järbe, 1971; Fried, 1974; Ueki and Fujiwara, 1977) or evoked catalepsy or ataxia (Grunfeld and Edery, 1969). Comparable doses of marihuana elicited lethargy and ataxia (Fried and Nieman, 1973; Rosenkrantz *et al.*, 1974). Massive oral Δ^9–THC doses depressed rats markedly (Thompson *et al.*, 1973b). It is worthwhile mentioning that the inhibition produced by doses near 1 mg/kg has often been preceded by excitation in rodents (Davis *et al.*, 1972; Rosenkrantz *et al.*, 1974; Weinberg *et al.*, 1977).

In contrast to the sensitivity of dogs to cannabis constituents, the mouse has usually required larger doses to evoke responses similar to those seen in other mammals. In general, single parenteral doses of Δ^9–THC greater than 10 mg/kg initiated hypoactivity, catalepsy, or ataxia (Grunfeld and Edery, 1969; Gill *et al.*, 1970; Phillips *et al.*, 1971; Sofia, 1972a). Similar findings were obtained by the s.c. or oral routes (Dewey *et al.*, 1970; Fairbairn and Pickens, 1979) except that no changes were reported by Ayhan *et al.* (1979).

Motor Activity after Repeated Treatment

Irritable aggressiveness was described as a consistent behavioral feature of monkeys given oral Δ^9–THC doses of 1 to 3 mg/kg for 2 yr (Sassenrath and Chapman, 1976). A similar behavior was not seen in the chimpanzee (Grilly *et al.*, 1973) or the baboon (Ames *et al.*, 1979). Chronic marihuana inhalation in monkeys induced intermittent depression (Coate and Voelker, 1979). In the dog, chronic exposure to marihuana smoke caused a general muscle weakness and decreased exploratory activity (Huy *et al.*, 1975a; Sullivan and Willard, 1978). Fear-retreat behavior was also described (Huy *et al.*, 1975a). Subacute i.v.

TABLE 3

Changes in Motor Activity in Animals Exposed to Marihuana or Δ^9–THC

Species[a]	Treatment			Behavioral Change	Reference
	mg/kg	days	route		
Baboon	10–30[b]	4–6 mo	p.o.	mild apathy	Ames *et al.*, 1979
Chimpanzee	1	2 yr	p.o.	scheduled performance ↓	Grilly *et al.*, 1973
Monkey	0.1	1	i.v.	sedation, huddling	Grunfeld and Edery, 1969
	5–45	28	i.v.	lethargy, huddled	Thompson *et al.*, 1974
	1–5	30	i.v.	avoidance ↓	Harris *et al.*, 1972
	6–14	1 yr	lungs	depression	Coate and Voelker, 1979
	1–32	1	i.p.	stimulation to depression	Scheckel *et al.*, 1968
	100–3,000	1	p.o.	hyperactivity to lethargy	Thompson *et al.*, 1973b
	1–3	2 yr	p.o.	aggressiveness	Sassenrath and Chapman, 1976
Dog	0.5	1	i.v.	stupor state	Grunfeld and Edery, 1969
	0.1–3	1	i.v.	sedation, ataxia	Dewey *et al.*, 1970, 1972b
	5	8	i.v.	depression, ataxia (tolerance)	Kaymakçalan and Deneau, 1972
	1–3	9 mo	lung	activity ↓	Huy *et al.*, 1975a
	1.4	1 yr	lungs	asthenia	Sullivan and Willard, 1978
	50–3,000	1	p.o.	sedation, ataxia	Thompson *et al.*, 1973b
Cat	5–15	1	i.v., i.p.	ataxia	Oskoui, 1971
	1	1	s.c.	ataxia, motor activity ↓	Kaymakçalan and Deneau, 1971

Rabbit	3–100	13	s.c.	activity ↓	Banerjee *et al.*, 1976
	15–150	28	s.c.	activity ↓	Thompson *et al.*, 1975
Rat	1–5	1	i.v.,i.p.,p.o.	bar pressing ↓	Henriksson and Järbe, 1971
	17	1–36	lungs	open field activity ↓	Fried and Nieman, 1973, 1976
	1–40	1	lungs	activity↓, ataxia	Rosenkrantz *et al.*, 1974
	1–4	87	lungs	'popcorn,' convulsions	Luthra *et al.*, 1976
	10–20	1	i.p.	catalepsy, ataxia	Grunfeld and Edery, 1969
	4–8	1	i.p.	activity wheel ↓	Fried, 1974
	1–10	1	i.p.	activity↓, catalepsy	Ueki and Fujiwara, 1977
	4–30	30	i.p.	hypersensitivity to depression	Phillips *et al.*, 1972
	200–2,000	1	p.o.	activity↓, ataxia	Thompson *et al.*, 1973b
	50–500	119	p.o.	'popcorn,' convulsions	Thompson *et al.*, 1973a
	2–50	6 mo	p.o.	'popcorn,' convulsions	Rosenkrantz *et al.*, 1975
Mouse	10–500	1	i.v., i.p.	ataxia, hypersensitivity	Phillips *et al.*, 1971
	10	1	i.p.	rotarod↓, catalepsy	Grunfeld and Edery, 1969
	25–200	1	i.p.	catalepsy	Gill *et al.*, 1970
	50–500	1	i.p.	activity ↓	Sofia, 1972a
	1–3	7–21	lungs	activity ↓	Weinberg *et al.*, 1977
	10	1	s.c.	activity ↓	Dewey *et al.*, 1970
	5–80	1	s.c.	no change	Ayhan *et al.*, 1979
	0.1	1	p.o.	catalepsy	Fairbairn and Pickens, 1979
Guinea pig	3	6 mo	i.p.	activity ↓	Huy *et al.*, 1975b

a. Various signs of suppressed motor activity have been seen in other mammals and nonmammals.
b. Dagga, 1.4% Δ^9-THC

treatments with Δ^9–THC doses of 1 to 15 mg/kg in monkeys induced lethargy, huddling ('thinker' posture), and sedation (Harris *et al.*, 1972; Thompson *et al.*, 1974). Delayed cumulative toxicity at a dose of 45 mg/kg resulted in instances of mortality (Thompson *et al.*, 1974). Repeated i.v. doses in dogs evoked depression (Kaymakçalan and Deneau, 1972). A slight transient and intermittent depression was observed in rabbits given large s.c. doses of Δ^9–THC (Thompson *et al.*, 1975; Banerjee *et al.*, 1976).

A biphasic pattern of locomotor inhibition and stimulation, and development of tolerance to both these effects, have been described in rats receiving 5 to 30 mg/kg (Davis *et al.*, 1972). Excitation of motor activity evoked by natural and synthetic Δ^9–THC in mice has been known for many years (Garriott *et al.*, 1967). Because dose and route of administration play key roles in pharmacological responses, and because not all animals within the same treatment group respond similarly, some investigators often do not observe the biphasic effects of cannabis components. However, during subacute or chronic investigations in rodents, tolerance development to CNS-inhibition has permitted recognition of states of CNS-stimulation. Such behavioral aberrations in rats have occurred after chronic marihuana exposure (Fleischman *et al.*, 1975; Luthra *et al.*, 1976) or in response to similar oral doses of Δ^9–THC (Rosenkrantz *et al.*, 1975) or after massive doses (Thompson *et al.*, 1973a). The sequence of behavioral events was similar for all routes of administration. Hyperactivity or hypersensitivity was detected at the low doses (0.7 to 2 mg/kg). At the higher doses (4 to 50 mg/kg), hypoactivity occurred in the first week, to which tolerance developed. The "popcorn" reaction (spontaneous vertical jumping) and fighting were subsequently discernible. Fighting was displayed by approximately 70% of the animals by weeks 6–7. Two peaks of the "popcorn" response, in weeks 3 and 8, involved 70% of the rats and correlated with two periods of delayed lethality. Of the affected rats, 30% died (Fleischman *et al.*, 1975). Tolerance to these neurotoxic signs developed thereafter. As mentioned previously, delayed deaths were also observed in monkeys treated with an i.v. Δ^9–THC dose of 45 mg/kg (Thompson *et al.*, 1974). In fact, 2 of 4 monkeys died and a 28-day i.v. LD_{50} of 45 mg/kg was estimated. After oral administration 2 of 8 monkeys were sacrificed moribund and a subacute $LD_{50} > 650$ mg/kg could be estimated.

A spectrum of excitation and inhibition has also been reported for mice (Phillips *et al.*, 1972). Others, using an interrupted smoking schedule for rodents, recorded decreased motor activity over 21–36 days of treatment (Fried, 1976; Weinberg *et al.*, 1977). Continuous exposure to marihuana reduced the motor activity of guinea pigs (Huy *et al.*, 1975b). Evidence concerning development of tolerance to motor aberrations and other behavioral anomalies has recently been reviewed (Fried, 1977; McMillan, 1977).

Comparison of changes in spontaneous motor activity in cannabinoid-treated animals and in human consumers of marihuana is not readily accomplished. Variability of pretest drug experience, psychosocial settings, and cultural customs confounds objective measurement of the drug effects on motor activity in humans (Braude and Szara, 1976; Dornbush and Kokkevi, 1976; Fried, 1977). Various types of distractions can influence the level of marihuana intoxication (Pihl *et al.*, 1977). Utilizing a respectable number of subjects, Babor *et al.* (1976) have demonstrated a decline in work and recreational activity during 3 wk of daily consumption of a known amount of marihuana (2% Δ^9–THC). Acute oral doses of Δ^9–THC (0.32 mg/kg) impaired manual dexterity and sensory reaction times (Belgrave *et al.*, 1979). The definite lethargy and sedation elicited by acute marihuana inhalation or by i.v. or oral administration of Δ^9–THC in human subjects is well documented but these findings are not particularly applicable for predicting adverse chronic effects on motor activity.

Electroencephalogram (EEG) Patterns

In general, one would expect more meaningful EEG data from subcortical electrode implants than from surface recordings. This consideration has restricted the usefulness of EEG studies in man. For studying drug effects, the advantage of placing electrodes in portions of the brain implicated in the control of a specific physiological function is obvious. In regard to environmental setting, it can be expected that EEG changes may vary with the state of alertness or drowsiness. An additional advantage of animal models is the capability of long-term implantation of electrodes with modest restraints of animal movement. It should be mentioned that EEG recordings were usually obtained about 15–60 min after treatment (Boissier, 1973; Fried, 1977) a time when the drug-induced behavioral effects are the most obvious.

EEG Changes in Man

Typical alterations in human EEG patterns (Table 4) induced by cannabis or Δ^9–THC (0.1–1 mg/kg) given via inhalation or orally have included an increase in alpha activity, a decrease in the peak frequency of alpha rhythm, and an increase in beta activity (Fink, 1976; Fink *et al.*, 1976). Desynchronization, although uncommon, has been reported (Deliyannakis *et al.*, 1970; Jones and Stone, 1970). Small oral doses of marihuana extract or Δ^9–THC often failed to elicit responses seen by the inhalation route (Hollister, 1971b; Deniker *et al.*, 1974). Changes in theta activity have been variable (Ames, 1958; Koukkou and Lehmann,

TABLE 4

EEG Patterns in Humans Exposed to Cannabis Constituents

Cannabis Preparation	Treatment[a,b] mg/kg	days	route	EEG Change	Reference
Hashish	0.5–1	chronic	lungs	slow waves ↑, fast waves ↓	Miras, 1969
Hashish	0.5–1	chronic	lungs	desynchronization	Deliyannakis *et al.*, 1970
Hashish	1–3	chronic	lungs	alpha ↑, beta ↓	Fink, 1976
Marihuana	0.1	chronic	lungs	desynchronization	Jones and Stone, 1970
Marihuana	0.1	1	lungs	alpha rhythm ↑	Rodin and Domino, 1970
Marihuana	0.1–0.3	1	lungs	alpha ↑, beta ↓	Volavka *et al.*, 1971
Marihuana	0.1	1	lungs	α–peak power ↓	Low *et al.*, 1973
Marihuana	0.3	1	lungs	alpha ↑	Roth *et al.*, 1973
Marihuana	0.2–0.6	1	lungs	frequency rates change	Linton *et al.*, 1975
Extract, Δ^9–THC	0.5	1	oral	little change	Hollister, 1971b
Δ^9–THC	10	3	oral	anomalies	Boissier, 1973
Δ^9–THC	0.7–1	1	oral	α amplitude ↑	Tassinari *et al.*, 1973
Δ^9–THC	0.1	1	oral	little change	Deniker *et al.*, 1974
Δ^9–THC	0.2	1	oral	alpha ↑, theta ↓	Koukkou and Lehmann, 1976

a. Relative potency based on Δ^9–THC; THC estimates for hashish assumes 5% THC content if latter not given.
b. Chronic treatment refers to subjects who have used cannabis for many years.

1976). Changes related to sleep EEG profiles and somatosensory evoked responses have also yielded somewhat variable results (Karacan *et al.*, 1976; Kopell *et al.*, 1978). The question as to why chronic cannabis users can continue to display changes in EEG when tolerance is known to develop to such alterations remains unanswered.

EEG Changes in Animals

Given the advantage of indwelling subcortical electrodes in animals, chronic responses to cannabis products can be measured more readily (Table 5). In the monkey, single i.v. treatments of Δ^9–THC caused spike responses at low doses (1 to 2 mg/kg) or epileptiform activity at doses above 5 mg/kg (Boyd *et al.*, 1971; Martinez *et al.*, 1972). Repeated small oral doses of Δ^9–THC diminished slow wave activity (Adams and Barratt, 1974) while a Δ^9–THC dose greater than 12 mg/kg in a marihuana extract induced protracted trains of 20–25 cps in thalamus and cerebellar nuclei (Stadnicki *et al.*, 1974a). Oral doses above 35 mg/kg caused 1.5–2 cps slow waves in hippocampus, amygdala and septum. Polyspike or epileptiform activities were not seen with the larger doses of marihuana extract. Tolerance developed to the EEG changes after 50 treatments. Serious subcortical EEG anomalies were observed in monkeys exposed to marihuana smoke for 6 mo (Heath, 1976; Heath *et al.*, 1979). The septal region was particularly prone to bursts of high amplitude spindles.

EEG synchrony and polyspike phenomena have also been observed in cats given modest doses of Δ^9–THC. Single i.p. injections of 2 to 4 mg/kg elicited synchronization of the EEG (Lipparini *et al.*, 1969; Hockman *et al.*, 1971). This is consistent with the observation that single i.v. injections of Δ^9–THC reduced the minimum alveolar concentration of halothane required for anesthesia (Stoelting *et al.*, 1973). Similar doses induced an increase in the frequency of long and short afterdischarges (Feeney *et al.*, 1973) and an enhancement of 12 cps activity (Wallach and Gershon, 1973). Chronic administration of Δ^9–THC initiated persistent slow wave changes in the mid-lateral cortex and spiking in the ectosylvian cortex (Barratt and Adams, 1973).

EEG patterns in rabbits reflected spike and wave complexes and changes in cortical voltage. Single i.v. Δ^9–THC doses of 1 to 10 mg/kg or multiple doses in one day gave rise to trains of spikes and waves (Lipparini *et al.*, 1969; Fujimori *et al.*, 1973; Willinsky *et al.*, 1973). Cortical voltage output was increased (Consroe, 1973). The rat responded to cannabinoids with an increase in EEG desynchronization, with the intermittent occurrence of high-voltage polyspikes (Lipparini *et al.*, 1969; Fried and Nieman, 1973). Prolonged oral treatment with doses of 10 to 40 mg/kg revealed the persistence of spike and high voltage spindle activ-

TABLE 5

EEG Patterns in Animals after Marihuana or Tetrahydrocannabinol

Species	Treatment			Manifestation	Reference
	mg/kg	days	route		
Monkey	2–4	6 mo	lung	subcortical anomalies	Heath, 1976; Heath *et al.*, 1979
	1.5	1	i.v.	cortical spikes	Boyd *et al.*, 1971
	1–13	1	i.v.	high voltage waves ↑	Martinez *et al.*, 1972
	12–38	50	oral	20–25 cps wave bursts	Stadnicki *et al.*, 1974
	1.2	60	oral	slow wave activity ↓	Adams and Barratt, 1974
Cat	1–10	1	i.p.	synchrony ↑	Lipparini *et al.*, 1969
	4.0	1	i.p.	synchrony ↑; spikes	Hochman *et al.*, 1971
	1–8	1	i.p., i.v.	12 Hz activity ↑	Wallach and Gershon, 1973
	1.5	10	oral	after discharge ↑	Feeney *et al.*, 1973
	2.7	180	oral	changes related to cortical area	Barratt and Adams, 1972
Rabbit	1–10	1	i.v.	spike and wave complexes	Lipparini *et al.*, 1969
	2	1	i.v.	biphasic ↑↓; limbic spikes	Fujimori *et al.*, 1973
	1–4	1	i.v.	spike and wave complexes	Willinsky *et al.*, 1973
	1	1	i.v.	cortical voltage ↑	Consroe, 1973
Rat	4–18	1	lung	spike and wave complexes	Fried and Nieman, 1973
	1–10	6	i.p.	synchrony ↑; wave bursts	Lipparini *et al.*, 1969
	10–40	5–35	oral	high voltage spindles	Pirch *et al.*, 1972
	10	90	oral	transient spike bursts	Stadnicki *et al.*, 1974

ities (Pirch *et al.*, 1972; Stadnicki *et al.*, 1974b). The latter investigators suggested that the "polyspike" phenomenon observed in the rat may be due in part to the surgical trauma of electrode implantation, but that Δ^9-THC enhanced the expression of "polyspike" activity.

The EEG findings in animals indicate that the hippocampus, amygdala, and septal areas are more sensitive to cannabinoids than the cortex is. Subcortical bursts of spike activity related to behavioral or motor manifestations are probably a more reliable index of cannabinoid action than EEG changes not associated with known biological effects of cannabis products.

Neurochemistry

Extensive investigations into the fundamental constituents of brain tissue as well as neurotransmitters have taken place in cannabinoid-treated animals (Nahas, 1976; Nahas and Paton, 1979). Because of the dramatic behavioral effects of cannabis components in the CNS, the biogenic amines have received considerable attention. Unfortunately, the maze of experimental designs has given rise more to disparities than to a definitive picture of the interactions of cannabis with the CNS (Bensemana and Gascon, 1974; Sabelli *et al.*, 1974).

A considerable number of studies have provided the opportunity to relate toxic or pharmacological effects to changes in concentration or turnover rate of neurotransmitters in brain (Table 6). With such an approach, a more meaningful interpretation of variable findings may at least be possible. Single treatments with Δ^9-THC (1 to 10 mg/kg) given by the i.v. or i.p. routes have reduced serotonin (5-hydroxytryptamine (5-HT)) levels during the period when monkeys are demonstrating behavioral symptoms of CNS inhibition ✓(Ho *et al.*, 1972). In contrast, Δ^9-THC increased 5-HT levels in rats (Schildkraut and Efron, 1971; Taylor and Fennessy, 1979) and mice (Holtzman *et al.*, 1969; Welch *et al.*, 1971) coincident with toxic signs of catalepsy or hypothermia. Larger doses by the s.c. route evoked the same change (Johnson *et al.*, 1976). Rat temperament also affected the 5-HT response (Palermo Neto and Carvalho, 1973).

Repeated administration of cannabinoids is associated with the confounding problem of tolerance development. It would appear that at the height of toxic manifestation, changes in 5-HT levels occur. When CNS-inhibition was still evident, 5-HT levels were elevated (Sofia *et al.*, 1977; Pradhan *et al.*, 1979). When CNS-stimulation (muricidal activity or hypersensitivity) was expressed, 5-HT levels were reduced (Ouellet *et al.*, 1973; Fujiwara and Ueki, 1974). The development of tolerance may in part explain unchanged 5-HT values (Aulakh *et al.*, 1980). However,

TABLE 6

Changes in Brain Content of Serotonin (5–HT) and Acetylcholine (ACh) and Toxic Signs in Animals Given Tetrahydrocannabinols

Species	Treatment			Changes in Behavior and Neurotransmitter System		Reference
	mg/kg	days	route	toxic signs	neurochemical change	
Monkey	1–10	1	i.v.	sedation	localized 5–HT ↓	Ho *et al.*, 1972
Rat	2	1	i.v.	hypothermia	5–HT ↑	Taylor and Fennessy, 1979
	1–5	1	i.v.,i.p.	vocal.; catalepsy	5–HT ± 0	Gallager *et al.*, 1972
	10	1	i.p.	catalepsy	5–HT ↑	Schildkraut *et al.*, 1971
	10	1	i.p.	muricide	5–HT ↓	Fujiwara and Ueki, 1974
	5–50	1	i.p.	hypothermia	5–HT ± 0	Yagiela *et al.*, 1973
	10–20	1–10	i.p.	depression	5–HT ↑	Pradhan *et al.*, 1979
	20	5–6	i.p.	depression	synthesis 5–HT ↑	Sofia *et al.*, 1977
	10	30	i.p.	hypersensitivity	5–HT ↓	Ouellet *et al.*, 1973
	10	34	i.p.	hyperactivity	5–HT ± 0	Aulakh *et al.*, 1980
Mouse	1–100	1	i.p.	hypothermia	5–HT ↑	Holtzman *et al.*, 1969
	10	1	i.p.	hypothermia	5–HT ↑	Welch *et al.*, 1971
	10–100	1	s.c.	hypothermia	5–HT ↑	Johnson *et al.*, 1976
	50	90	p.o.	hypothermia	5–HT ↑	Anton *et al.*, 1974
Rat	5	1	i.v.	depression	ACh, ACHE ↓	Askew *et al.*, 1974
	0.2–10	1	i.v.	catalepsy	ACh, turnover ↓	Revuelta *et al.*, 1978

	10–30	1	i.p.	depression	ACh, turnover ↑	Maitre, 1971
	10	1	i.p.	depression	ACh ↑	Brown, 1973
	6	1	i.p.	muricide	ACh ± 0	Yoshimura *et al.*, 1974
	5–10	8	i.p.	hyperactivity	synthesis ACh ↓	Friedman *et al.*, 1976
	1–30	1	i.p.	depression	ACh ↑	Domino *et al.*, 1979
	20	1	p.o.	hypothermia	AChE ± 0	Moss *et al.*, 1978
	2–50	28	p.o.	hyperactivity	AChE ↓	Luthra *et al.*, 1976
Mouse	10	1	i.p.	hyperactivity	ACh ± 0	Welch *et al.*, 1971
	100	1	i.p.	depression	ACh ↑	Karbowski *et al.*, 1975

subchronic administration of a large dose via the oral route produced prolonged hypothermia and 5–HT levels were increased (Anton *et al.*, 1974).

Despite the presence of toxic signs, other investigators did not find a change in 5–HT levels after a single injection (Gallager *et al.*, 1972; Yagiela *et al.*, 1974). This discrepancy may in part be due to the drug formulations used. Gallager *et al.* (1972) used a serum matrix which may have impeded the release of Δ^9–THC (see Table 2), while Yagiela *et al.* (1974) utilized an aqueous emulsion which behaves like a drug depot when given by the i.p. route (Rosenkrantz *et al.*, 1972). The restricted bioavailability of drug may have coincidentally provided sufficient drug concentrations to elicit peripheral toxic responses but an inadequate dose level to affect 5–HT in the whole brain.

Acetylcholine (ACh) and the activity of acetylcholinesterase (AChE) have also been measured after cannabinoid treatment (Table 6). Apparently contradictory results have been obtained in rodents. After a single treatment with a modest THC dose, motor depression was associated with either a decline (Askew *et al.*, 1974) or elevation (Brown, 1973; Karbowski *et al.*, 1975; Domino *et al.*, 1979) in ACh levels. ACh turnover rate was stimulated (Maitre, 1971) or inhibited (Revuelta *et al.*, 1978a) and no change in AChE activity was discerned (Moss *et al.*, 1978). Hyperactivity was associated with a decrease in the synthesis of ACh (Friedman *et al.*, 1976) and no change in ACh levels (Welch *et al.*, 1971; Yoshimura *et al.*, 1974). Subacute oral treatment reduced AChE activity during hyperactivity (Luthra *et al.*, 1976).

Other biogenic amines have been implicated in cannabinoid action (Table 7). Norepinephrine (NE) levels were diminished in discrete areas of the monkey brain after modest single doses of Δ^9-THC (Ho *et al.*, 1973) but whole-brain levels of NE or 5–HT were unaltered (Ho and Johnson, 1976). Suppressed motor activity and hypothermia were associated with decrements of brain NE of rodents given a single 10 to 50 mg/kg dose of Δ^9–THC (Ho *et al.*, 1972; Ho and Johnson, 1976) despite stimulation of NE synthesis (Hershkowitz and Szechtman, 1979; Bloom and Kiernan, 1980). Doses near 5 mg/kg generally did not alter NE or dopamine (DA) levels (Yagiela *et al.*, 1973; Bracs *et al.*, 1975; Taylor and Fennessy, 1977). Very large single doses initiated hypothermia and elevated NE levels in mice (Holtzman *et al.*, 1969).

Subacute administration parenterally or orally produced behavioral signs of CNS-inhibition associated with localized reductions of NE levels (Pradhan *et al.*, 1979), an increase in NE synthesis (MacLean and Littleton, 1977), and localized increases in monoamine oxidase (MAO) activity (Banerji *et al.*, 1977). During the phase of CNS-stimulation, NE and DA levels were unchanged (Mazurkiewicz-Kwilecki and Filczewski, 1973; Colombini *et al.*, 1974; Aulakh *et al.*, 1980). On the other hand, the activities of both MAO and tyrosine hydroxylase were increased (Ho *et al.*, 1973; Ouellet *et al.*, 1973).

Too few studies have been performed with gamma-aminobutyric acid (GABA) to reveal a consistent pattern of changes (Table 7). Low doses of Δ^9–THC did not change GABA levels in rat brain during the periods of CNS-inhibition (Revuelta *et al.*, 1978b). A large single dose decreased GABA levels (Leonard, 1971) and a repeated modest dose increased GABA levels in the presence of catalepsy (Edery and Gottesfeld, 1975).

Putting aside for the moment variations in species and experimental design, ascertainment of a neurotransmitter profile is complicated by the pattern of distribution of active drug or metabolite at appropriate concentrations in brain areas susceptible to cannabinoids. Changes in neurotransmitter levels in responsive portions of the brain might be more meaningful in understanding the bimodal pharmacological and toxicological effects of cannabis products and the development of tolerance. Indeed, attempts in this direction have been made for the parameters of EEG and tolerance. Shannon and Fried (1972) related EEG changes in the rat to distribution of bound and unbound radioactive Δ^9–THC. Disposition of tracer was primarily in the extra-pyramidal motor system and some limbic structures and 0.8% of the total injected drug was weakly bound in the brain and presumably accounted for the EEG changes. Dewey *et al.* (1976a) investigated the subcellular distribution of Δ^9–THC in tolerant and nontolerant animals. Interestingly, brain cannabinoid levels were lower in tolerant than in nontolerant dogs and pigeons. In contrast, concentrations in rodent brains were higher in the tolerant state.

4. CARDIOVASCULAR TOXICITY

The increase in heart rate within a few minutes after smoking marihuana is well documented for humans (Hardman and Hosko, 1976). Variability in blood pressure responses has been attributed to postural factors. That difference exists between human and animal cardiovascular responses to cannabinoids is evident from the observations of tachycardia in humans and bradycardia in animals. However, under certain circumstances of stress, oral doses of Δ^9–THC have evoked bradycardia in humans (Perez-Reyes *et al.*, 1973a). An inversion of heart rate response in animals, tachycardia occurring before bradycardia, has also been observed (Dewey *et al.*, 1972b; Huy *et al.*, 1974; McLendon *et al.*, 1976). Despite these cardiovascular variations, CNS-

TABLE 7

Changes in Brain Content of Norepinephrine (NE), Dopamine (DA), γ-Aminobutyric Acid (GABA) and Monoamine Oxidase (MAO) and Toxic Signs in Animals Given Tetrahydrocannabinols

Species	Treatment			Changes in Behavior and Catecholamine System		Reference
	mg/kg	days	route	toxic sign	neurochemical change	
Monkey	1–10	1	i.v.	sedation	localized NE ↓	Ho *et al.*, 1972
Rat	0.1–5	1	i.v.	hypothermia	NE, DA ± 0	Taylor and Fennessy, 1977
	2	7	i.v.	hyperactivity	NE ± 0	Mazurkiewicz-Kwilecki and Filczewski, 1973
	10	10	i.v.	hyperactivity	Tyr hydroxylase ↓	Ho *et al.*, 1973
	5–50	1	i.p.	hypothermia	NE ± 0	Yagiela *et al.*, 1973
	10	5	i.p.	depression	localized NE ↓	Pradhan *et al.*, 1979
	10	14	i.p.	sedation	synthesis NE ↑	MacLean and Littleton, 1977
	10–50	15	i.p.	depression	localized MAO ↑	Banerji *et al.*, 1977
	10	30	i.p.	hypersensitivity	MAO ↑	Ouellet *et al.*, 1973
	10	34	i.p.	hyperactivity	NE, DA ± 0	Aulakh *et al.*, 1980
	10	1	p.o.	hypothermia	NE, DA ± 0	Bracs *et al.*, 1975
Mouse	1–50	1	i.v.	depression	localized NE ↓	Ho *et al.*, 1972
	10	1	i.v.	tail pinch ↓	synthesis NE, DA ↑	Hershkowitz *et al.*, 1979
	2–16	1	i.v.	hypothermia	synthesis NE, DA ↑	Bloom and Kiernan, 1980
	>100	1	i.p.	hypothermia	NE ↑	Holtzman *et al.*, 1969
	10–150	15	s.c.	hyperactivity	NE ± 0	Colombini *et al.*, 1974

Rat	0.2–5	1	i.v.	depression	GABA ± 0	Revuelta *et al.*, 1978
	100	1	i.p.	depression	GABA ↓	Leonard, 1971
	20	14	i.p.	catalepsy	GABA ↑	Edery and Gottesfeld, 1975

inhibition via higher centers has been the common finding in animals given cannabis products (Adams *et al.*, 1974).

Effects of a Single Treatment

The administration of cannabinoids to humans or animals produced alterations of the heart rate which were first observed within a few minutes and peaked between 20 and 30 min after smoking or when the i.v. route was used. A delayed peak response occurred after administration by other routes. Alterations in heart rate and blood pressure persisted for several hours before returning to normal. Accompanying the tachycardia elicited by marihuana in man were other cardiovascular effects related to autonomic actions (Table 8).

Tachycardia in man was readily documented (Renault *et al.*, 1971; Galanter *et al.*, 1972; Clark *et al.*, 1974), and other investigators found EKG changes after inhalation of marihuana (Beaconsfield *et al.*, 1972) or Δ^9–THC given orally (Kochar and Hosko, 1973). Changes in heart rate were associated with inhibited vascular reflexes (Roth *et al.*, 1973), decreased peripheral vascular resistance (Savary *et al.*, 1974; Malit *et al.*, 1975; Benowitz *et al.*, 1979), or increased cardiac index (Malit *et al.*, 1975; Gash *et al.*, 1978). The cardiovascular responses to cannabinoids appear to be brought about through sympathetic stimulation and parasympathetic inhibition. In general, changes in blood pressure in man were dependent on posture, the mean pressure being slightly elevated in the supine position and diminished in the upright position irrespective of route of cannabinoid administration (Waskow *et al.*, 1970; Johnson and Domino, 1971; Weiss *et al.*, 1972; Benowitz *et al.*, 1979).

Cardiovascular responses to cannabinoids in animals have been primarily bradycardia and hypotension (Tables 8 and 9). A single behaviorally relevant i.v. dose of Δ^9–THC in monkeys has been shown to produce bradycardia (Kaymakçalan and Deneau, 1971) and to suppress cardiac conditioned responses necessary to sustain homeostasis (McLendon *et al.*, 1976). In conscious or anesthetized dogs, a single Δ^9–THC dose of approximately 0.1 to 5 mg/kg induced bradycardia and reduced blood pressure (Kubena *et al.*, 1971; Lahiri *et al.*, 1972; Friedman *et al.*, 1977). Associated with these cardiovascular effects were decreased cerebral blood flow (Beaconsfield *et al.*, 1972), decreased heart contractility (Cavero *et al.*, 1973, 1974; Brannan *et al.*, 1975), and decreased heart output (Bright *et al.*, 1975). In general, cardiovascular responses in anesthetized cats were similar to those in dogs for the same dose and route of administration (Hosko and Hardman, 1971; Barnard, 1973; Graham and Li, 1973; Vollmer *et al.*, 1974). Also observed were reduced cardiac discharges (Daskalopoulos *et al.*, 1975), contractility (Oskoui

TABLE 8

Cardiovascular Effects of Marihuana or Tetrahydrocannabinols in Man and Monkey

Species	Treatment			Cardiovascular Response	Reference
	mg/kg	days	route		
Man	0.01–0.1	1	lungs	tachycardia	Renault *et al.*, 1971
	0.1	1	lungs	tachycardia, blood pressure ↑	Johnson and Domino, 1971
	0.1	1	lungs	tachycardia, EKG change, BP ± 0	Beaconsfield *et al.*, 1972
	0.1	1	lungs	tachycardia	Galanter *et al.*, 1972
	0.1	1	lungs	tachycardia, inhibited vascular reflexes	Roth *et al.*, 1973
	0.1	1	lungs	peripheral vasodilation	Savary *et al.*, 1974
	0.2	1	lungs	tachycardia	Clark *et al.*, 1974
	0.1	1	lungs	ventricular performance increased	Gash *et al.*, 1978
	0.1–0.2	1	i.v.	cardiac index ↑, peripheral resistance ↓	Malit *et al.*, 1975
	0.04	1	i.v.	vascular resistance ↓, BP ↑	Benowitz *et al.*, 1979
	0.3	1	p.o.	tachycardia, BP ↓	Waskow *et al.*, 1970
	0.3	1	p.o.	tachycardia, BP ↑	Weiss *et al.*, 1972
	3–4	1	p.o.	tachycardia, EKG change	Kochar and Hosko, 1973
	2–4	1	p.o.	tachycardia, forearm blood flow ↓	Benowitz *et al.*, 1979
Monkey	6–14	365	lungs	daily transient bradycardia	Coate and Voelker, 1979
	0.2–1	1	i.v.	cardiac conditioned responses ↓	McLendon *et al.*, 1976
	1–10	1	i.v.	bradycardia	Kaymakçalan and Deneau, 1971
	2	21	i.v.	bradycardia, blood pressure ↓	Fredericks and Benowitz, 1977
	5–45	28	i.v.	bradycardia (tolerance)	Thompson *et al.*, 1973b

TABLE 9

Cardiovascular Effects of Marihuana or Tetrahydrocannabinols in Dogs, Cats and Other Species

Species	Treatment			Cardiovascular	
(condition)	mg/kg	days	route	Response	Reference
Dog	2–4	270	lungs	tachycardia (partial tolerance)	Huy *et al.*, 1975a
	1.4	365	lungs	bradycardia (tolerance)	Sullivan and Willard, 1978
(anesth.)	5	1	i.v.	bradycardia, BP ↓	Kubena *et al.*, 1971
(anesth.)	0.1	1	i.v.	cerebral blood flow ↓	Beaconsfield *et al.*, 1972
	2	1	i.v.	bradycardia	Lahiri *et al.*, 1972
(anesth.)	0.1–5	1	i.v.	heart contractility ↓, HR ↓, BP ↓	Cavero *et al.*, 1973, 1974
(anesth.)	0.5	1	i.v.	heart contractility ↓, HR ↓, BP ↓	Brannan *et al.*, 1975
(anesth.)	0.5	1	i.v.	cardiac output ↓, blood pH ↓	Bright *et al.*, 1975
	0.1–0.3	1	i.v.	bradycardia, BP ± 0	Friedman *et al.*, 1977
	5	8	i.v.	bradycardia (partial tolerance)	Kaymakçalan and Deneau, 1972
	0.5–5	10	i.v.	tachycardia or bradycardia	Dewey *et al.*, 1972b
	1	7	s.c.	hemodynamics normal	Jandhyala and Buckley, 1977
	2	35	s.c.	bradycardia (tolerance)	Jandhyala, 1978
Cat					
(anesth.)	0.2	1	i.v.	bradycardia, BP ↓	Graham and Li, 1973
(anesth.)	3–10	1	i.v.	bradycardia, BP ↓	Barnard, 1973
(anesth.)	2	1	i.v.	bradycardia, BP ↓	Vollmer *et al.*, 1974
(anesth.)	0.03–0.3	1	i.v.	HR ↓, BP ↓, cardiac discharges ↓	Daskalopoulos *et al.*, 1975
(anesth.)	1	1	i.v.	bradycadia, BP ↓	Hosko and Hardman, 1976
(anesth.)	2.5	1	i.v.	HR ↓, BP ↓, contractility ↓	Oskoui and Hofmann, 1976
(anesth.)	1–2	1	i.v.	baroreceptor responses ↓	Schmeling and Hosko, 1978

Rat	1–4	87	lungs	bradycardia (partial tolerance)	Fleischman *et al.*, 1975
	1–3 μg	1	cerebral ventricle	tachycardia	Jones *et al.*, 1980
	5–20	1	i.v.	bradycardia, BP ± 0	Milzoff *et al.*, 1971
	1	1	i.v.	subcortical blood flow ↓	Goldman *et al.*, 1975
	0.03–0.3	1	i.v.,i.p.	tachycardia to bradycardia	Manno and Manno, 1975
	0.1–3	1	i.v.	bradycardia, BP ↓	Adams *et al.*, 1976
(pithed)	0.3–3	1	i.v.	HR, BP ± 0	Earnhardt and Adams, 1976
(anesth.)	1	1	i.v.	bradycardia, BP ↓	Li and Chung, 1978
(anesth.)	2–10	1	i.v.	BP ↓ to BP ↑ to BP ↓	Siqueira *et al.*, 1979
	0.1–0.5	1	i.p.	tachycardia, BP ± 0	Osgood and Howes, 1977
	0.1–10	13	i.p.	bradycardia (tolerance)	Hine *et al.*, 1977
	6	10	i.p.	bradycardia to tachycardia	Kawasaki *et al.*, 1980
	20	1	s.c.	hypotension	Williams *et al.*., 1973
	10	16	s.c.	bradycardia (no tolerance)	Kaymakçalan, 1974
	2–50	180	p.o.	bradycardia (tolerance)	Rosenkrantz *et al.*, 1975
Rabbit	2.5–10	1	i.v.	bradycardia, BP ↓	Barnard, 1973
Bat	200	1	i.p.	bradycardia, vasodilation	Brown *et al.*, 1974

and Hofmann, 1976), and responses of baroreceptors (Schmeling and Hosko, 1978).

Except for pithed rats (Earnhardt and Adams, 1976), both conscious and anesthetized rats exhibited bradycardia and hypotension at reasonable cannabinoid doses by various routes of administration (Milzoff *et al.*, 1971; Williams *et al.*, 1973; Adams *et al.*, 1976; Li and Chung, 1978). On the other hand, tachycardia has been elicited with Δ^9–THC or its 11-OH metabolite at doses less than 0.5 mg/kg when given i.v., i.p. or s.c. (Manno and Manno, 1975; Osgood and Howes, 1977) or by intracerebral ventricular injection (Jones *et al.*, 1980). Subcortical blood flow was reduced by 1 mg/kg Δ^9–THC given i.v. (Goldman *et al.*, 1975). Siqueira and coworkers (1979) closely monitored rat blood pressure after a single i.v. injection of Δ^9–THC and found a triple effect reflected in an immediate hypotension of short duration followed by a transient hypertension that reverted to a sustained hypotension after 5 min. The intermediate phase was attributed to direct vasoconstriction, while hypotension was ascribed to changes in vagal and sympathetic tonus.

With i.v. doses of Δ^9–THC near 10 mg/kg, bradycardia and lowered blood pressure were discerned in rabbits (Barnard, 1973). Reduced blood pressure in bats receiving massive i.p. doses of Δ^9–THC was related to vasodilatation (Brown *et al.*, 1974).

Effects of Repeated Treatments

Chronic use of cannabis in humans has not resulted in permanent alterations in cardiovascular functions (Dornbush *et al.*, 1976). Repeated oral i.v. administrations of Δ^9–THC in humans have resulted in development of tolerance to cannabinoid-induced tachycardia (Benowitz and Jones, 1975; Benowitz *et al.*, 1979).

Repeated doses of marihuana or Δ^9–THC in monkeys evoked bradycardia in the first week or two, larger doses initiating tolerance (Thompson *et al.*, 1973b; Fredericks and Benowitz, 1977). Prolonged exposure of monkeys to marihuana smoke induced a transient bradycardia which appeared daily after drug administration (Coate and Voelker, 1979).

In contrast, prolonged exposure to marihuana in dogs elicited transient tachycardia with the development of partial tolerance at Δ^9–THC doses of 2 to 4 mg/kg (Huy *et al.*, 1975a) and bradycardia and tolerance at 1.4 mg/kg (Sullivan and Willard, 1978). Although both groups of investigators used female beagles of similar weights, Huy *et al.* (1975a) introduced the smoke through a tracheostomy while Sullivan and Willard

(1978) used a face mask for inhalation. The former smoking technique, although not natural, would permit a greater dose to be delivered with little loss of cannabinoids in the buccal cavity or nasal turbinates. When Dewey *et al.* (1972b) repeatedly injected similar Δ^9–THC doses by the i.v. route, an initial tachycardia was seen that soon converted to a sustained bradycardia. Partial tolerance to bradycardia has been reported for dogs (Kaymakçalan and Deneau, 1972). Repeated s.c. treatment for 35 days revealed bradycardia to which tolerance developed (Jandhyala, 1978). On the other hand, a shorter interval of treatment by the s.c. route failed to evoke hemodynamic aberrations (Jandhyala and Buckley, 1977).

Marihuana inhalation in rats for 87–365 days induced a persistent bradycardia to which there was partial development of tolerance (Fleischman *et al.*, 1975, 1979). Relevant repeated doses of Δ^9–THC via the i.p. (Hine *et al.*, 1977; Kawasaki *et al.*, 1980), s.c. (Kaymakçalan and Sivil, 1974) or oral route (Rosenkrantz *et al.*, 1975) caused bradycardia for several days and tolerance developed at the larger doses soon after. Crude marihuana extracts given for 14 days also elicited bradycardia and hypotension in rats, with subsequent tolerance development (Graham and Li, 1973; Thompson *et al.*, 1973a). Kawasaki *et al.* (1980) clearly observed the emergence of tachycardia after the bradycardia phase. It is of interest that an oral Δ^9–THC dose of 25 mg/kg given for 10 days decreased blood pressure in spontaneously hypertensive rats without the development of tolerance (Kosersky, 1978).

That alteration in heart rate can occur without parallel aberrations in blood pressure suggests that the cardiac and peripheral vascular effects of cannabinoids are mediated by different neuronal pathways, or that the two types of effect have different dose requirements. Modulation of sympathetic and parasympathetic systems at supraspinal levels appears to be the mechanism of cannabis action.

5. RESPIRATORY TOXICITY

From the earliest experiments with cannabis constituents, the severe CNS-inhibition produced by toxic doses pointed to disturbance of central control of respiratory function. That cannabinoid therapy for asthma was entertained was based on the bronchodilator activity of cannabis products, but the rationale was contrary to known adverse effects of cannabinoids and the phenomenon of tolerance (Bellville *et al.*, 1975; Graham *et al.*, 1976; Hollister, 1979; Tennant, 1979). In general, under controlled experimental conditions in humans and laboratory animals, respiratory toxicity induced by cannabis components can be observed (Table 10).

TABLE 10

Marihuana or Tetrahydrocannabinol Effects on the Respiratory System of Man and Animals

Species	Treatment			Change in Respiratory System	Reference
	mg/kg	days	route		
Man	0.4	1	lungs	decreased airway resistance	Vachon *et al.*, 1973
	0.3	1	lungs, p.o.	airway dilatation	Tashkin *et al.*, 1973
	0.3	1	lungs, p.o.	depressed respiration	Bellville *et al.*, 1975
	1–3	20	lungs	disturbed pulmonary functions	Mendelson *et al.*, 1976
	0.3	50	lungs	airway obstruction	Tashkin *et al.*, 1976
	0.5–3	60	lungs	narrower airways	Cohen, 1976
	1[a]	3,650	lungs	no significant changes	Cruickshank, 1976
Monkey	6–14	365	lungs	transient depressed respiration	Coate and Voelker, 1979
	5–45	28	i.v.	depressed respiration (tolerance)	Thompson *et al.*, 1974
Dog	1.4	365	lungs	bronchiolitis	Sullivan and Willard, 1978
	2–4	912.5	lungs	depressed respiration rate	Roy *et al.*, 1976
	5	1	i.v.	depressed respiration rate	Kubena *et al.*, 1971
	0.1–0.5	1	i.v.	alveolar halothane conc. decreased	Stoelting *et al.*, 1973
	0.5	1	i.v.	lung compliance reduced	Bright *et al.*, 1975
	5	8	i.v.	respiration rate ↓ (partial tolerance)	Kaymakçalan and Deneau, 1972
	> 150	1	p.o.	respiration rate depressed	Thompson *et al.*, 1973b
Cat	0.2	1	i.v.	respiration rate depressed	Graham and Li, 1973

Rat	2–40	1	lungs	respiration rate depressed	Rosenkrantz *et al.*, 1974
	0.7–4	87	lungs	respiration rate ↓ (tolerance)	Fleischman *et al.*, 1975
	5–20	1	i.v.	respiration rate depressed	Milzoff *et al.*, 1971
	10–80	1	i.v.	respiration rate depressed	Rosenkrantz *et al.*, 1974
	1–2	1	i.p.	alveolar cyclopropane conc. decreased	Vitez *et al.*, 1973
	> 100	1	p.o.	respiration rate depressed	Thompson *et al.*, 1973b
	> 50	119	p.o.	respiration rate ↓ (tolerance)	Thompson *et al.*, 1973a
	2–50	180	p.o.	respiration rate ↓ (tolerance)	Rosenkrantz *et al.*, 1975

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a. Jamaican ganja.

Effects of a Single Treatment

Earliest observations of cannabinoid effects in humans described a potentially beneficial bronchodilation and decreased airway resistance (Tashkin *et al.*, 1973; Vachon *et al.*, 1973). However, Bellville and coworkers (1975) reported a depressed respiration after marihuana smoking or oral ingestion of Δ^9–THC.

Single i.v. administration of Δ^9–THC to dogs reduced respiration rate (Kubena *et al.*, 1971) and lung compliance (Bright *et al.*, 1975). Massive oral doses depressed the respiratory rate to the point of apnea (Thompson *et al.*, 1973b). Inhibition of respiration was also common in cats (Graham and Li, 1973).

Irrespective of route of administration, cannabinoids decreased respiration rates in rats (Milzoff *et al.*, 1971; Thompson *et al.*, 1973b; Rosenkrantz *et al.*, 1974). As in dogs, minimum alveolar concentration of an anesthetic was reduced in rats by Δ^9–THC (Vitez *et al.*, 1973).

In most instances hypopnea was dose-related, and with large doses apnea resulted in death. Resuscitation has been successful in monkeys and rats (Rosenkrantz and Braude, 1974; Rosenkrantz, unpublished data). Subsequent unpublished observations of this group suggest that cardiac arrest contributes more to lethality than respiratory depression does. Toxic doses of CBD, CBCh, hashish oil, and crude marihuana extracts generally depress respiration but in some instances an initial stimulation of respiration occurred in monkeys (Rosenkrantz *et al.*, 1981).

Effects of Repeated Treatments

Conflicting findings on cannabinoid-induced respiratory toxicity exist for human marihuana consumers (Dornbush *et al.*, 1976). Whereas habitual users of ganja (usually with tobacco) were reported not to exhibit adverse effects on respiratory function (Cruickshank, 1976), controlled volunteer studies have revealed airway obstruction (Cohen, 1976; Tashkin *et al.*, 1976) and disturbed pulmonary function (Mendelson *et al.*, 1976; Tashkin *et al.*, 1978). Morphologic changes in chronic hashish users have been documented (Tennant, 1979).

Prolonged treatment of animals with marihuana smoke or Δ^9–THC administered i.v. or orally has consistently decreased respiration rate and has caused pulmonary irritation. Thompson *et al.* (1974) have shown that tolerance develops to cannabinoid-induced respiratory depression in monkeys. Coate and Voelker (1979) observed a transient but persistent daily decrease in respiration among monkeys exposed to marihuana smoke for one year. In the dog, extended marihuana treatment has resulted in inhibited respiration (Kaymakçalan and Deneau, 1972) and the development of bronchiolitis (Roy *et al.*, 1976; Sullivan and Willard, 1978).

Findings similar to those seen in dogs were obtained for rats inhaling marihuana smoke or receiving Δ^9–THC orally for periods of treatment beyond 85 days (Table 10). Thus, respiration rate was depressed for 10– 15 days, followed by the appearance of tolerance to this effect of cannabinoids (Thompson *et al.*, 1973a; Fleischman *et al.*, 1975; Rosenkrantz *et al.*, 1975). Morphologic aberrations of lungs were evident after approximately 80 days of treatment.

6. TEMPERATURE ALTERATIONS

Interruption of thermoregulation by cannabis products has been a more consistent phenomenon in animal models than in human subjects (Haavik *et al.*, 1976). Thermic responses have depended on dose, environmental temperature, and duration of treatment (Table 11). In general, relevant or large doses have evoked hypothermia in animals, especially at lower ambient temperatures. Prolonged treatment with appropriate doses led to the development of tolerance to this effect (Kaymakçalan and Deneau, 1971; Kaymakçalan *et al.*, 1977). The usual small doses of Δ^9–THC present in marihuana or given orally to man elicit little change or measurable hypothermia (Waskow *et al.*, 1970; Hollister, 1971b; Hosko *et al.*, 1973; Dornbush *et al.*, 1976).

Hyperthermic Response

Single doses of Δ^9–THC between 0.1 and 4 mg/kg administered i.v. or i.p. to rats induced an elevation in rectal temperature (Sofia, 1972b; Johansson *et al.*, 1974; Fennessy and Taylor, 1978). Similar repeated doses as discrete injections of Δ^9–THC or as marihuana smoke also elicited hyperthermia to which tolerance developed over many weeks (Fleischman *et al.*, 1975; Rosenkrantz *et al.*, 1975). The hyperthermic response was observed within 15–30 min, sooner after marihuana inhalation, and temperatures returned to normal limits within a few hours (Sofia, 1972b; Fleischman *et al.*, 1975).

Hypothermic Response

Curiously, the hyperthermic effect of low doses of Δ^9–THC seen in rats has not been a paramount observation in monkeys, dogs, cats, or mice (Table 11). Instead, a dose-related hypothermia has been evident (Kaymakçalan and Deneau, 1971). After single administration of modest or large doses of Δ^9–THC, monkeys (Haavik and Hardman, 1973), dogs

TABLE 11

Marihuana or Tetrahydrocannabinol Effects on Thermoregulation in Animals

Species	Treatment mg/kg	Treatment days	Treatment route	Changes in Rectal Temperature	Reference
Monkey	6–14	365	lungs	no significant change	Coate and Voelker, 1979
	1–10	1	i.v.	hypothermia	Kaymakçalan and Deneau, 1971
	2–30	1	i.v.	hypothermia	Haavik and Hardman, 1973
	5–45	28	i.v.	transient hypothermia (tolerance)	Thompson *et al.*, 1974
Dog	5	8	i.v.	hyperthermia/hypothermia (partial tolerance)	Kaymakçalan and Deneau, 1972
	1.4	365	i.v.	no significant change	Sullivan and Willard, 1978
	>100	1	p.o.	mild hypothermia	Thompson *et al.*, 1973b
Cat	0.5–2	1	i.v.	hypothermia	Schmeling *et al.*, 1980
	1	1	i.v.	hypothermia	Kaymakçalan and Deneau, 1971
Rat	2–40	1	lungs	hypothermia	Rosenkrantz *et al.*, 1974
	0.7–4	87	lungs	hyper- and hypothermia (tolerance)	Fleischman *et al.*, 1975
	0.1–5	1	i.v.	hyper- and hypothermia	Fennessy and Taylor, 1978
	0.1–2	1	i.p.	hyper- and hypothermia	Sofia, 1972b
	5	1	i.p.	hypothermia (females more)	Borgen *et al.*, 1973
	1	1	i.p.	hyperthermia	Johansson *et al.*, 1974
	10	1	i.p.	hypothermia	Schmeling and Hosko, 1977
	5–10	10	i.p.	hypothermia (tolerance)	Rating *et al.*, 1972
	10–50	5	s.c.	hypothermia	Fernandes *et al.*, 1974

Rat	10–40	15	s.c.	hypothermia (tolerance)	Kaymakçalan *et al.*, 1977
	>50	119	p.o.	hypothermia (tolerance)	Thompson *et al.*, 1973a
	2–50	180	p.o.	hyper- and hypothermia (tolerance)	Rosenkrantz *et al.*, 1975
Mouse	2–32	1	i.v.	heat production ↓, heat loss ↑	Haavik and Hardman, 1973
	4–32	1	i.v.	heat production ↓, heat loss ↑	Arora and Hardman, 1974
	2–16	1	i.v.	hypothermia	Bloom *et al.*, 1978
	5–50	1	i.p.	hypothermia	Phillips *et al.*, 1971
	5–50	1	i.p.	heat production ↓, heat loss ↑	Yagiela *et al.*, 1973
	20	1	i.p.	oxygen consumption decreased	Pertwee and Tavendale, 1979
	>50	30	i.p.	hypothermia (tolerance)	Liu, 1974
	10–100	1	i.m.	hypothermia	Abel, 1973
	0.3–40	15	s.c.	hypothermia	Uran *et al.*, 1980

(Thompson *et al.*, 1973b), and cats (Schmeling *et al.*, 1980) responded with hypothermia. Repeated treatments in these species also evoked hypothermia in the first week or two, after which tolerance developed (Kaymakçalan and Deneau, 1971; Thompson *et al.*, 1974). In contrast, prolonged marihuana inhalation of Δ^9–THC doses in excess of 1 mg/kg did not disrupt thermoregulation in monkeys (Coate and Voelker, 1979) or dogs (Sullivan and Willard, 1978).

In rodents, the hypothermic response to a single treatment was elicited by 1 to 10 mg/kg introduced via the lungs (Rosenkrantz *et al.*, 1974), i.v. (Bloom *et al.*, 1978; Fennessy and Taylor, 1978), i.p. (Phillips *et al.*, 1971; Sofia, 1972b; Borgen *et al.*, 1973; Schmeling and Hosko, 1977) and i.m. (Abel, 1973). The hypothermic response was greater in females than males (Borgen *et al.*, 1973), and was more marked when the animals' activity was low (Abel, 1973; Pertwee and Tavendale, 1979). Furthermore, the intensity of temperature response decreased as ambient temperature increased (Haavik and Hardman, 1973). Hypothermia was related to diminished heat production, increased heat loss, and decreased oxygen consumption (Haavik and Hardman, 1973; Yagiela *et al.*, 1973; Arora and Hardman, 1974; Pertwee and Tavendale, 1979). Some evidence exists that Δ^9–THC and its 11-OH metabolite, but not CBN or CBD, exert their influence in the thermoregulatory area of the hypothalamus and modulate autonomic outflow through regulation of catecholamine synthesis (Schmeling and Hosko, 1977; Bloom *et al.*, 1978; Davies and Graham, 1980).

Both rats and mice exhibited hypothermia after prolonged treatment. Repetitive large doses of marihuana smoke evoked hypothermia for many days until tolerance occurred (Fleischman *et al.*, 1975). The development of tolerance often revealed a phase of hyperthermia which also diminished with time. Multiple treatments with modest doses of Δ^9–THC by the i.p. (Rating *et al.*, 1972), s.c. (Fernandes *et al.*, 1974; Kaymakçalan *et al.*, 1977; Uran *et al.*, 1980), or oral route (Thompson *et al.*, 1973a; Rosenkrantz *et al.*, 1975) in rats or the i.p. route in mice (Liu, 1974) initiated hypothermia to which tolerance developed after 7–14 days of treatment.

7. GROWTH AND DIET CHANGES

The problem of documenting real changes in growth rates among experienced chronic marihuana or hashish consumers is not easily resolved. Few or no clinical histories exist on subjects before their encounter with cannabis. Restriction of cannabis use for a few weeks before commencing with a controlled drug intake in no way eliminates irreversible changes in the form of lost growth gains or drug-modified dietary adjustments already in effect. In animal models, alterations in food consumption may not necessarily reflect changes in appetite but may be a measure of altered behavioral activity. That changes in food consumption and body weights in animals are produced by cannabinoids cannot be disputed (Table 12). Moreover, disturbances of endocrine function may play a key role in modulation of growth (Rosenkrantz and Esber, 1980).

Changes in Growth Rates

The ratio of final body weight (at the end of an observation period or at necropsy) to initial body weight (usually just before drug treatment) provides a satisfactory index of growth rate. From this definition, it can be discerned that experimental models must be observed for a few days, even after a single treatment, in order to obtain a suitable measurement of growth gain or loss.

Single Treatment

Δ^9–THC injected i.p. into monkeys (Scheckel *et al.*, 1968) or given orally to humans had no significant effect on body weight (Hollister, 1971b). Dewey *et al.* (1972b) reported emaciation and loss in body weight of a mongrel dog given a Δ^9–THC dose of 60 mg/kg i.v. A similar finding at oral doses greater than 200 mg/kg was obtained in beagles (Thompson *et al.*, 1973b).

A reduced growth rate occurred for rats given a single Δ^9–THC dose (1 to 5 mg/kg) i.p. (Glick and Milloy, 1972; Järbe and Henriksson, 1973) but not orally (Anderson-Baker *et al.*, 1979).

Multiple Treatments

In a study of heavy and casual marihuana users, Greenberg *et al.* (1976) found a dose-related gain in weight during the first five days of a 21-day treatment period. Habitual Costa Rican marihuana users reported episodes of involuntary weight loss (Coggins *et al.*, 1976). Chronic exposure of monkeys to marihuana smoke failed to affect growth rate (Coate and Voelker, 1979) whereas subacute i.v. administration of Δ^9–THC consistently diminished growth rate at doses above 15 mg/kg (Thompson *et al.*, 1974). In dogs, chronic exposure to marihuana smoke reduced body weight and growth rate (Huy and Roy, 1976; Sullivan and Willard, 1978).

Extended treatment of rodents with marihuana or Δ^9–THC generally reduced growth rate although some tolerance developed to this effect (Table 12). In rats 6–30 i.p. injections of Δ^9–THC at doses between 5 and 15 mg/kg depressed growth rate (Abel and Schiff, 1969;

TABLE 12

Effects of Marihuana or Tetrahydrocannabinols on Growth of Man and Animals

Species	Treatment			Effects on Growth Rates		Reference
	mg/kg	days	route	food intake	body weight	
Man	0.1	21	lungs	caloric intake ↑	increased	Greenberg *et al.*, 1976
	0.1	3,650	lungs	appetite ↑	transient weight loss	Coggins *et al.*, 1976
	0.5	1	p.o.	appetite, food ↑	no change	Hollister, 1971b
Monkey	6–14	365	lungs	no change	no change	Coate and Voelker, 1979
	5–45	28	i.v.	anorexia	slowed growth	Thompson *et al.*, 1974
	1–32	1	i.p.	food and water ↓	little change	Scheckel *et al.*, 1968
Dog	1.4	365	lungs	(rationed)	decreased	Sullivan and Willard, 1978
	4–8	900	lungs	food increased	slowed growth	Huy and Roy, 1976
	>200	1	p.o.	anorexia	decreased	Thompson *et al.*, 1973b
Rat	0.7–4	87	lungs	anorexia	slowed growth	Fleischman *et al.*, 1975
	0.5–2	1	i.p.	food and water ↓	(food deprivation)	Glick and Milloy, 1972
	1–5	1	i.p.	food and water ↓	decreased	Järbe and Henriksson, 1973
	15	6	i.p.	food decreased	slowed growth	Abel and Schiff, 1969
	2–5	9	i.p.	food and water ↓	decreased	Sofia and Knobloch, 1976
	5–10	10	i.p.	food decreased	decreased	Rating *et al.*, 1972
	1	12	i.p.	food and water ↑	(food deprivation)	Gluck and Ferraro, 1974
	2.5	23	i.p.	food ± 0, water ↓	no change	Sjödén *et al.*, 1973
	4,8	30	i.p.,p.o.	food ↓, water ± 0	decreased	Manning *et al.*, 1971
	4–30	30	i.p.	(not studied)	decreased growth	Phillips *et al.*, 1972
	4	1	p.o.	transient decline	no significant change	Anderson-Baker *et al.*, 1979

Rat	>50	119	p.o.	anorexia to food, water ↑	decreased growth	Thompson *et al.*, 1973a
	2–50	180	p.o.	anorexia to food ↑	decreased growth	Rosenkrantz *et al.*, 1975
	10–50	5	s.c.	anorexia	slowed growth	Fernandes *et al.*, 1974
Mouse	1–3	21	lungs	(not studied)	decreased growth	Weinberg *et al.*, 1977
Rabbit	3–100	13	s.c.	anorexia	decreased growth	Thompson *et al.*, 1975
	15–150	28	s.c.	anorexia	decreased growth	Banerjee *et al.*, 1976
Guinea pig	3	180	i.p.	(not studied)	decreased growth	Huy *et al.*, 1975b

Manning *et al.*, 1971; Phillips *et al.*, 1972; Sofia and Knobloch, 1976). Alterations in growth rate may be overlooked in experiments involving food deprivation as part of the protocol (Gluck and Ferraro, 1974), or when growth rates are measured only after tolerance to the hypophagic effect has developed (Rating *et al.*, 1972). Curiously, Sjödén *et al.* (1973) obtained losses of body weight with Δ^8–THC and not Δ^9–THC. Inhibited growth was also elicited with larger doses of Δ^9–THC given by the s.c. (Fernandes *et al.*, 1974) or oral route (Thompson *et al.*, 1973a; Rosenkrantz *et al.*, 1975). Depressed growth rates were common among rats chronically exposed to marihuana smoke (Fleischman *et al.*, 1975, 1979). Cannabis extract (50 mg/kg), i.p. for 14–30 days, also depressed the growth rate (Graham and Li, 1973; Gupta *et al.*, 1974).

Similar suppression of growth rates has been reported for mice exposed for 21 days to marihuana smoke (Weinberg *et al.*, 1977). Δ^9–THC given i.p. or s.c. decreased growth rates in rabbits (Thompson *et al.*, 1975; Banerjee *et al.*, 1976) and guinea pigs (Huy *et al.*, 1975b). It is worth mentioning that the cannabinoid-inhibited growth loss has persisted during 14- to 30-day recovery periods in some studies (Manning *et al.*, 1971; Thompson *et al.*, 1973a; Fleischman *et al.*, 1975; Rosenkrantz *et al.*, 1975). There was a trend for the posttreatment body weights of treated animals to catch up to those of controls but not quite to achieve control values.

Changes in Food Consumption

The anecdotal descriptions of stimulated appetite among marihuana consumers are well known. Hollister's (1971b) attempt to substantiate this observation under controlled experimental conditions revealed increased food intake in approximately 50% of the subjects after drug treatment. Unfortunately, there is a paucity of creditable data on food consumption and body weights of chronic cannabis users before and after cannabis consumption (Hollister, 1971b; Abel, 1975). In the case of animal models, variation in experimental protocols has resulted in opposing changes of food and water intake (Table 12). Tolerance to cannabis-induced changes in food intake has been studied (Rating *et al.*, 1972; Corcoran and Amit, 1974).

Single Treatment

In the human responders to oral Δ^9–THC, there were indications of increased food consumption (Hollister, 1971b). On the other hand, much larger i.p. doses in monkeys decreased food and water intake (Scheckel *et al.*, 1968). Massive oral doses in dogs induced anorexia (Dewey *et al.*, 1972b; Thompson *et al.*, 1973b).

Among rodents, acute treatment with relevant doses of Δ^9–THC decreased food and usually water consumption more when given by the i.p. route (Glick and Milloy, 1972; Järbe and Henriksson, 1973) than when administered orally (Anderson-Baker *et al.*, 1979). In sheep, small i.v. doses of Δ^9–THC stimulated food intake at 30 min postdrug (Baile *et al.*, 1978).

Multiple Treatments

Costa Rican cannabis users of 10 yr duration reported intermittent episodes of both appetite stimulation and anorexia (Coggins *et al.*, 1976). Loss of interest in diet was related to frequent symptoms of indigestion, nausea, and abdominal pain. In controlled subacute experiments, Greenberg *et al.* (1976) demonstrated an increase in caloric intake in man.

Chronic exposure of monkeys to marihuana smoke did not alter food consumption (Coate and Voelker, 1979). On the contrary, i.v. Δ^9–THC for 28 days consistently induced anorexia in this species (Thompson *et al.*, 1974). In the dog, Huy and Roy (1976) observed early signs of anorexia but after two years of exposure to marihuana smoke, there was a stimulation of food intake.

Several investigators have observed the transformation of an initial decrease in food consumption to a phase of increased food intake during prolonged treatment. Thus, depending on the duration of treatment, some researchers predominantly observed decreased food and/or water consumption (Abel and Schiff, 1969; Manning *et al.*, 1971; Rating *et al.*, 1972; Fernandes *et al.*, 1974; Sofia and Knobloch, 1976) while others detected a phase of increased food consumption (Thompson *et al.*, 1973a; Gluck and Ferraro, 1974; Rosenkrantz *et al.*, 1975). A similar finding was made for a cannabis extract (Graham and Li, 1973). Depending on the dose and the route of administration, conversion from the inhibitory phase to the stimulatory phase occurred between 7 and 20 days.

In the rabbit, s.c. injections of large doses of Δ^9–THC for 13–28 days induced anorexia (Thompson *et al.*, 1975; Banerjee *et al.*, 1976).

Attempts have been made to relate glucose stores to changes in dietary needs and to cannabinoid effects on catecholamine levels. In humans, cannabis inhalation in chronic users decreased blood lactate without influencing blood glucose levels (Papadakis *et al.*, 1974). Subchronic treatment of monkeys with i.v. Δ^9–THC also did not alter blood glucose levels, but liver glycogen content was depressed (Sprague *et al.*, 1973). Furthermore, depletion of liver glycogen was observed in rabbits treated s.c. with large doses of Δ^9–THC and in rats exposed once to excess marihuana smoke.

8. ORGAN FUNCTION AND MORPHOLOGY

Since the preponderance of whole animal studies was conducted with short-term administration of cannabinoids, it is not surprising that few alterations of organ function, weight, or morphology were encountered in such investigations. On the other hand, it was reasonable to anticipate disturbances in lung tissue when the inhalation route was used because of the usual irritating qualities of smoke. Furthermore, it should be recalled that the large doses are deliberately chosen for toxicological studies and adverse effects are not unexpected.

The interpretation of organ function changes in marihuana users has generally been compromised because of polydrug use. Variability in response also confounds interpretation. The hepatotoxicity in humans reported by Kew *et al.* (1969) occurred in three of 12 cases. Limitation in the number of subjects impedes interpretation. King and Cowen (1969) observed changes in hematology and renal function in two cases. In other isolated cases of verified cannabis poisoning, incomplete data hampered an extensive evaluation of organ-specific toxicity (Heyndrickx *et al.*, 1969; Hochman and Brill, 1971; Nahas, 1971; Bro *et al.*, 1975). Initiation of pulmonary irritation in marihuana and hashish consumers is well documented (Renault *et al.*, 1974; Tennant, 1979). The new technique of computer-assisted axial tomography did not confirm an earlier report of cerebral atrophy in man (Kuehnle *et al.*, 1977). Irritation of the oral mucosa has been seen (Warnock and Shalla, 1977).

In animal models, the facility of scheduled necropsies and the advantages of varied species and larger numbers of subjects provide a greater opportunity of relating cannabinoid dosage to adverse effects. Even under this favorable climate, some disparities of findings have occurred (Table 13).

Changes in Organ Weights

Changes in organ weights have been expressed in several ways: (i) absolute weight, (ii) as a percentage of final body weight, and (iii) as a ratio with brain weight. Expression of relative organ weights as a percentage of final body weight in part corrects for circumstances of altered general growth rate (i.e., due to dehydration, anorexia, increased metabolism). Because of the distinct possibility of cannabinoid effects on reproductive processes (Nahas and Paton, 1979; Rosenkrantz, 1979; Harclerode, 1980; Rosenkrantz and Esber, 1980), the following

TABLE 13

Organ Weight Changes Related to Treatment of Animals with Marihuana and Tetrahydrocannabinols

Species	Treatment			Change in Organ Weight and Direction (A, absolute; R, relative)	Reference
	mg/kg	days	route		
Monkey	6–14	365	lungs	no significant changes	Coate and Voelker, 1979
	5–45	28	i.v.	liver ↑(R), thymus ↓(R)	Thompson *et al.*, 1974
	50–500	28	p.o.	liver ↑(R), thymus ↓(R), adrenal ↑(R)	Thompson *et al.*, 1974
Dog	1.4	365	lungs	weight data not given	Sullivan and Willard, 1978
	4–8	900	lungs	lung ↓(A), heart ↑(A), brain ↑(A)	Huy and Roy, 1976
	4–8	900	lungs	no change in lung weight (R)	Roy *et al.*, 1976
Rabbit	3–100	13	s.c.	liver ↓(R), lung ↓(A)	Banerjee *et al.*, 1976
	15–150	28	s.c.	liver ↓(R)	Thompson *et al.*, 1975
Guinea pig	3	180	i.p.	liver ↓(R), heart ↓(A), spleen ↓(R)	Huy *et al.*, 1975b
Rat	0.7–4	23	lungs	adrenals ↑(R)	Rosenkrantz and Braude, 1974
	0.1–0.5	42	lungs	no significant changes	Ho *et al.*, 1971a
	0.7–4	87	lungs	lung, heart ↑(R); prostate, testis ↓(R)	Fleischman *et al.*, 1975
	4–30	30	i.p.	liver and lungs ↓(A)	Phillips *et al.*, 1972
	50–500	119	p.o.	prostate, ovary, uterus, spleen ↓(R)	Thompson *et al.*, 1973a
	2–50	180	p.o.	lungs, kidneys, heart, liver ↑(R)	Rosenkrantz *et al.*, 1975

discussion of organ weight changes is subcategorized into major organs and those related to the reproductive tract.

Major Organs

No significant changes in organ weights were perceived in monkeys chronically inhaling large doses of marihuana smoke (3–4 cigarettes per day) (Coate and Voelker, 1979). In contrast, modest Δ^9–THC doses i.v. or massive doses given orally to monkeys for 28 days increased the relative weights of liver and adrenals and decreased the weight of the thymus gland (Thompson *et al.*, 1974). Development of tolerance in the chronic study may in part explain the discrepancy. Chronic marihuana inhalation in dogs also did not reveal significant changes in relative organ weights (Roy *et al.*, 1976; Sullivan and Willard, 1978). However, absolute weights of heart and brain were increased and lung weight decreased after 30 mo of marihuana exposure (Huy and Roy, 1976).

Among rodents treated with a wide range of dosage by various routes of administration, significant changes in organ weights have occurred (Table 13). Large s.c. doses of Δ^9–THC in rabbits depressed liver weights (Thompson *et al.*, 1975; Banerjee *et al.*, 1976). A similar effect was seen in guinea pigs treated with small doses i.p. for a much longer period of time (Huy *et al.*, 1975b). In addition, relative spleen weight declined. Marihuana or Δ^9–THC doses comparable to those used by humans caused no significant organ weight changes in rats exposed to smoke for 42 days (Ho *et al.*, 1971a). Larger, but relevant, doses inhaled for a longer period of time increased relative weights of rat lung and heart (Fleischman *et al.*, 1975). Absolute weights of rat lung and liver decreased after 30 i.p. injections of Δ^9–THC at doses above 20 mg/kg (Phillips *et al.*, 1972). By the oral route, multiple intubations of Δ^9–THC induced elevations in absolute or relative weights of lungs, kidneys, heart, and liver (Thompson *et al.*, 1973a; Rosenkrantz *et al.*, 1975; Manno *et al.*, 1977).

In general, absolute and relative adrenal weights increased as a reflection of nonspecific stress irrespective of the route of administration (Thompson *et al.*, 1973a; Rosenkrantz and Braude, 1974; Fleischman *et al.*, 1975; Rosenkrantz *et al.*, 1975). However, the magnitude of change diminished with duration of treatment, probably indicating a state of tolerance or other adjustment to the stress. For other organ weights, a time-related pattern of intensity of change may emerge. A greater increase or decrease of specific organ weights occurred at 180 days compared with 90 days after oral Δ^9–THC (Rosenkrantz *et al.*, 1975). On the other hand, the extent of changes diminished at 87 inhalations compared with 27 or 57 inhalations of marihuana smoke (Fleischman *et al.*, 1975). Occasionally, the direction of change was inverted with time and some organ weight changes were sex-related (i.e., those of spleen and pancreas). In general, organ weights returned to normal limits after a 30-day recovery interval.

Reproductive/Endocrine Organs

The interaction of marihuana and cannabinoids with endocrine glands and the reproductive tract in humans and animals has recently been the subject of extensive reviews (Nahas and Paton, 1979; Rosenkrantz, 1979; Rosenkrantz and Esber, 1980; Smith, 1980; Bloch, this volume). Essentially, cannabis-induced reduction of gonadal weights has been associated with oligospermia or morphological anomalies but has not always correlated with hormonal imbalance. Generally, neither gross appearance of testes nor sexual appetite has been affected by modest doses of marihuana or Δ^9–THC in humans. In animals, prolonged treatment with relevant inhalation or oral doses has usually resulted in decreased relative weights of testis and prostate in rodents (Thompson *et al.*, 1973a; Fleischman *et al.*, 1975; Rosenkrantz *et al.*, 1975; Nahas and Paton, 1979) and in monkeys (Thompson *et al.*, 1974). Other cannabinoids have reduced testicular size in rodents (Rosenkrantz and Hayden, 1979) and in monkeys (Rosenkrantz and Esber, 1980). Massive doses of Δ^9–THC, Δ^8–THC and crude marihuana extract have decreased rat ovarian and uterine weights (Thompson *et al.*, 1973a).

Morphological Alterations

Histopathological evaluations have been performed in several species treated with various products of cannabis. Particularly informative have been the morphological data from long-term toxicology studies in which scheduled necropsies were performed several times during and after chronic treatment. Except for the respiratory tree and testis, relevant doses of marihuana or Δ^9–THC have had little or no effect on the morphology of most organs examined by means of light microscopy. Autopsy specimens from humans have been rare and definitive assessments of microanatomical anomalies are lacking.

It is worthwhile to note that repeated s.c. applications of large doses of Δ^9–THC in rabbits induced ulceration and granulomatous inflammation (Thompson *et al.*, 1975; Banerjee *et al.*, 1976). Injection site necrosis was also evident after repeated i.v. injections of Δ^9–THC in monkeys (Thompson *et al.*, 1974). Applications of marihuana or hashish smoke condensates or tars to mouse skin have produced signs of carcinogenicity including metaplasia of the skin and skin tumors (Magus and Harris, 1971; Cottrell *et al.*, 1973; Procter *et al.*, 1974; Hoffman *et al.*, 1975; Szepsenwol *et al.*, 1979).

Major Organs

Massive single oral doses of Δ^9–THC, Δ^8–THC and crude marihuana extract in monkeys, dogs, and rats did not produce definite drug-related lesions in major organs (Thompson *et al.*, 1973b). In the rat, hypocellularity of the spleen and congestion of thymus and adrenal glands were common. Congestion of many major organs was also found in monkeys receiving a single i.v. Δ^9–THC dose greater than 100 mg/kg (Thompson *et al.*, 1974).

Subacute i.v. administration of Δ^9–THC (45 mg/kg) to monkeys produced thymus atrophy and liver congestion (Thompson *et al.*, 1974). Vacuolization of hepatocytes and accumulation of pleomorphic eosinophilic inclusion bodies were indicative of liver degeneration. Repeated oral doses (500 mg/kg) in monkeys were associated with atrophy of the pancreas, ulcerative colitis, myeloid hyperplasia of the bone marrow, and vacuolar nephrosis. Monkeys and dogs chronically exposed to marihuana smoke had minimal morphologic changes (Sullivan and Willard, 1978; Coate and Voelker, 1979). Deposition of pigment was observed in nodular lymphoid tissue of dogs (Sullivan and Willard, 1978). More serious have been the anomalies reported in electron micrographs of brain tissue from monkeys chronically exposed to marihuana smoke (Heath *et al.*, 1979). Among the findings were widened synaptic clefts, clumping of synaptic vesicles, a high incidence of nuclear inclusions, and reduced volume density of the rough endoplasmic reticulum. The alterations occurred predominantly in the septal, hippocampal, and amygdalar regions where the greatest changes in EEG patterns were seen after cannabinoid treatment. In the classical dog studies with "red oil," Walton *et al.* (1938) found instances of cerebral hyperemia. Brain damage has been reported in dogs given crude resin (Durandina and Romasenko, 1972).

Morphological alterations induced by cannabinoids have been found more frequently in rats after repeated treatments. Subacute i.p. injection of Δ^9–THC (30 mg/kg) for 30 days caused liver hyperplasia with an increase in hyperchromatic hepatic cells (Phillips *et al.*, 1972). Massive oral doses of Δ^9–THC, Δ^8–THC, or crude marihuana extract given to rats for 119 days produced splenic hypocellularity and vacuolization of the adrenal gland (Thompson *et al.*, 1973a). Instances of bone hypocellularity were also noted. Chronic oral treatment (90–180 days) at more modest doses (10–50 mg/kg) failed to produce drug-related lesions (Rosenkrantz *et al.*, 1975). Organ disruption in rats was also minimal after exposure to marihuana smoke for 23 days (Rosenkrantz and Braude, 1974), 87 days (Fleischman *et al.*, 1975), or one year (Fleischman *et al.*, 1979).

In the guinea pig, chronic i.p. injections of Δ^9–THC (3 mg/kg) were only associated with a decrease in liver glycogen and the presence of fat globules in the adrenal gland (Huy *et al.*, 1975b). Subacute treatment of rabbits with hashish, or of hamsters with Δ^9–THC, has affected bone marrow or produced other lesions (Janzen *et al.*, 1978; Joneja and Kaiserman, 1978).

Pulmonary Pathology

Recognition of the disastrous effect of marihuana and hashish smoke on the respiratory tree has been slow in coming. That introduction of cannabinoids by parenteral or oral routes may evoke similar harmful pulmonary effects cannot be discounted because of the unusual affinity of pure cannabinoids for lung tissue (Thompson *et al.*, 1974; Rosenkrantz and Fleischman, 1979). The pioneering efforts of Tennant and coworkers have revealed a close relationship between hashish consumption and deleterious lung changes in humans (Tennant, 1979). The predominant morphological anomalies included squamous metaplasia, basal cell hyperplasia, and the presence of other atypical cells. It is not surprising that lung changes were more intense in smokers using a combination of hashish and tobacco. In any case, pulmonary aberrations were very similar to those frequently associated with subsequent initiation of emphysema and carcinoma.

After relatively shorter periods of exposure compared with the human study, marihuana smoke in monkeys (Coate and Voelker, 1979) and dogs (Sullivan and Willard, 1978), did not induce morphological changes in the lungs. However, prolongation of marihuana inhalation in dogs beyond two years clearly caused an 87% incidence of pulmonary squamous metaplasia (Roy *et al.*, 1976). Macrophage infiltration into the walls of terminal air passages was associated with bronchiolitis. Large repeated i.v. doses of Δ^9–THC in monkeys (Thompson *et al.*, 1974) or dogs (Dewey *et al.*, 1972b) induced lung congestion, pulmonary hemorrhage and edema, and early signs of emphysema. Walton *et al.* (1938) also found pulmonary edema in dogs given "red oil."

Subchronic or chronic inhalation of relevant doses of marihuana in rats produced lung congestion, edema and focal hemorrhages (Rosenkrantz and Braude, 1974; Fleischman *et al.*, 1975, 1979). Pulmonary pathology was definitely related to dose after approximately 85 exposures. A focal alveolitis and pneumonitis progressed from mobilization of alveolar macrophages and foreign body cell inflammation to pronounced proliferative anomalies. Focal granulomata and cholesterol clefts became more evident as treatment continued (Rosenkrantz and Fleischman, 1979). Semiquantitation of focal aggregates of alveolar macrophages indicated this parameter was dose-related and was not reversible during a 30-day recovery period. Alveolar bactericidal activity was significantly reduced in rats inhaling marihuana smoke (Huber *et al.*, 1979). Even by the oral route, chronically administered Δ^9–THC in rats has been associated with pulmonary irritation (Rosenkrantz *et al.*, 1975).

Reproductive Tract

The early report on spermatogonial degeneration in rats treated with massive doses of cannabinoids (Thompson *et al.*, 1973a) has been confirmed with relevant doses of marihuana and pure cannabinoids (Nahas and Paton, 1979). That various cannabinoids can contribute to inhibition of spermatogenesis was demonstrated in rats exposed to Turkish marihuana, CBD, or CBCh (Rosenkrantz and Hayden, 1979). Epithelial degeneration of the seminiferous tubules with the presence of multinucleated giant cells was observed in Δ^9–THC-treated rats after 30 days (Phillips *et al.*, 1972). A small dose of crude marihuana extract produced testicular degeneration in dogs treated s.c. for 30 days (Dixit *et al.*, 1977).

There have been no substantiated reports of morphological changes in the female reproductive tract. Since effects on reproduction will be reviewed elsewhere in this text (see Bloch, this volume), no review of cannabinoid-altered biochemical constituents in the various components of the reproductive tracts will be considered here. Some pertinent investigations have recently been reviewed (Nahas and Paton, 1979; Rosenkrantz, 1979).

Organ Function Anomalies

By and large, no consistent cannabinoid-related alterations in hematology, hemochemistry, or urinalysis profiles have been established for human marihuana consumers (Dornbush *et al.*, 1976). Similarly, at relevant doses of marihuana or Δ^9–THC, deviations from normal among treated animals have been sparse (Fleischman *et al.*, 1975; Rosenkrantz *et al.*, 1975).

Blood Profile

As is usually the case, specific blood constituents were measured to assess organ function (i.e., blood urea nitrogen (BUN) for kidney, transaminases for liver, hormones for endocrine glands, etc.) or organ damage. One-year exposure of monkeys (Coate and Voelker, 1979) or dogs (Sullivan and Willard, 1978) to marihuana smoke did not significantly alter BUN, alkaline phosphatase, or transaminases. In the dog, concentrations of serum α_1-globulin and triglycerides were decreased (Huy *et al.*, 1975a). Hematological findings in large animal inhalation studies were unremarkable. Δ^9–THC given i.v. to monkeys for 28 days decreased calcium and chloride and caused hypochromic anemia and leukocytosis (Thompson *et al.*, 1974).

Subacute s.c. treatment of rabbits reduced serum potassium, BUN, alkaline phosphatase, and glucose (Banerjee *et al.*, 1976), only the latter two changes being confirmed in a different study (Thompson *et al.*, 1975). No disturbance of liver or kidney function was seen by Lukas and Temple (1974) under similar experimental conditions. Hematological values were normal in rabbit studies. Short-term inhalation of marihuana smoke in rats did not disrupt blood profiles (Ho *et al.*, 1971a; Rosenkrantz and Braude, 1974) although there was a trend toward reduced hematocrit values. Inhalation extending beyond 85 days did not produce blood aberrations (Fleischman *et al.*, 1975). On the other hand, Δ^9–THC given orally for six months produced elevations in transaminases, glucose, hematocrit, and red blood cell count (Rosenkrantz *et al.*, 1975). Fluctuations of transaminases and creatine phosphokinase activities were found in rats by Manno *et al.* (1977) after 28 days of treatment with small oral doses of Δ^9–THC. Massive subchronic oral doses increased serum glutamic-oxaloacetic transaminase activity and produced leukopenia (Thompson *et al.*, 1973a). In the guinea pig, Δ^9–THC reduced α_1-globulin and free fatty acids and increased γ globulins (Huy *et al.*, 1975b).

The functions of the reproductive tract and endocrine glands have been assessed by measurements of circulating hormone levels. Since this topic will be covered elsewhere in this book (see Bloch, this volume) reference is made only to recent reviews of pertinent material (Nahas and Paton, 1979; Rosenkrantz, 1979; Harclerode, 1980; Rosenkrantz and Esber, 1980; Smith, 1980).

Urinalysis

There has been little or no concrete evidence for the occurrence of urinary aberrations. Urinary patterns were generally normal in monkeys (Thompson *et al.*, 1974), rabbits (Banerjee *et al.*, 1976), and rats (Rosenkrantz *et al.*, 1975) given Δ^9–THC by various routes or in rats after inhalation of marihuana smoke (Rosenkrantz and Braude, 1974; Fleischman *et al.*, 1975).

9. DISCUSSION

Cannabinoid investigators have made conscious and honest efforts to mimic conditions of human cannabis usage in animal models in order to assess risk potential. Many researchers have also probed molecular events to uncover the mechanism(s) of cannabinoid actions. Although the latter endeavor has academic and medical importance, it is doubtful whether this sort of fundamental knowledge will persuade users to discontinue cannabis use. Given the stage of our current knowledge of cannabis toxicology, can we conclude that the findings in animal paradigms are applicable to humans? If so, can estimates of adverse risk to humans be propounded? If not, in what direction should new explorations proceed in order to attain a more precise estimate of risk?

The content of the present treatise confirms in more than a general manner that responses to cannabinoids in animals are closely similar to those in humans. Both behavioral aberrations and neurotoxicity were elicited by marihuana or pure cannabinoids, whether inhaled or administered orally. These routes of administration are the major methods of cannabis consumption in man. It should be expected that i.v. treatments would evoke responses similar to those produced by the inhalation route since both routes provide direct entrance to the systemic circulation and this has proven to be the case for Δ^9–THC ('spiked' placebo marihuana smoke vs pure i.v. Δ^9–THC). Therefore, one cannot escape the conclusion that human consumers of cannabis are confronted with undesirable side effects during acute or subacute usage. However, the seemingly larger doses used in animals suggest that the intensity of adverse effects encountered by humans would be much less than that of those experienced by animals. Such interpretation may be mere wishful thinking, however, since circulating levels of Δ^9–THC at behaviorally relevant dosages were similar in humans and animals (Rosenkrantz, 1979; Rosenkrantz and Fleischman, 1979; Ohlsson *et al.*, 1980). The "high" in humans and CNS-effects in animals had a time course corresponding to that of the plasma concentrations. Cannabinoids, given by i.v. injection or by smoking, produced initial responses within a few minutes that declined steadily over the next few hours. After oral treatment, responses were much slower in onset, of greater duration, and related to lower plasma concentrations (Ohlsson *et al.*, 1980).

That relevant doses appear to be metabolized and cleared readily should diminish apprehension about the use of cannabis. Unfortunately, at least four factors preclude such relaxation: (i) although plasma concentrations decrease with time, concentrations in organs, including brain and lungs, are on the rise; (ii) active metabolites form which prolong the duration of effect; (iii) tissue storage of cannabinoids is unusually prolonged; and (iv) chronic use of cannabis products raises the probability of induction of side-effects. Cumulative toxicity and delayed lethality have already been demonstrated in monkeys and rats (Thompson *et al.*, 1974; Fleischman *et al.*, 1975; Rosenkrantz *et al.*, 1975). It can be presumed that the development of tolerance affords protection against many of the toxic effects. However, it is not known if or when a state of tolerance will dissipate in the face of life-span use of cannabis. It has already been found that two separate episodes (after three and eight weeks of treatment) of neurotoxicity (as manifested by the "popcorn" response), and fighting aggression occur despite the development of tolerance during the first episode (Fleischman *et al.*, 1975; Luthra *et al.*, 1976).

On the other side of the ledger are the large safety factors based on acute and subacute LD_{50} values. Acute inhalation or i.v. LD_{50}s in rats and monkeys indicate a factor of approximately 500–1,000 in relationship to a human effective dose of 0.05 mg/kg. Subacute LD_{50}s in the same animal species reduce this factor to approximately 100–200. Extrapolation of such data related to the risk of lethality, however, in no way minimizes other nonlethal adverse side-effects such as those associated with aberrant behavior manifested by inhibited self-development and antisocial activities. Furthermore, the potential deterioration of organ function, particularly of the lungs and testes, with chronic use is a reality documented by inhalation studies in man and animals (Nahas and Paton, 1979; Rosenkrantz and Fleischman, 1979; Tennant, 1980).

Before an adequate balance sheet can be prepared of the beneficial, the innocuous and the deleterious effects of cannabis products, further chronic investigations must be performed. Of first priority is a life-span inhalation study in rodents. Higher mammals live too long to be useful for such research. Organ specimens should be examined by means of both light and electron microscopy. Other future studies should encompass reproductive, teratological, and hormone profile assessments in monkeys chronically exposed to marihuana smoke. The discrepancy between humans and animals with respect to immunosuppression should be resolved. In all studies where aberrant changes are discerned, suitable recovery intervals should be monitored in order to ascertain persistence or reversal of adverse effects.

Irritability, restlessness, and sleeplessness have been described as potential signs of cannabinoid withdrawal in humans and animals (Dornbush *et al.*, 1976; Nahas and Paton, 1979; Tulunay *et al.*, 1980; see also Jones, this volume). These cannabis-related symptoms should receive a more quantitative examination. The relationship between tolerance to effects on organ function and change in cannabinoid levels in the organs should be evaluated. Such data may reveal the extent of protection afforded by the state of tolerance and why tolerance develops at different rates to different cannabinoid-induced effects (Dewey *et al.*, 1976b; Rosenkrantz and Braude, 1976). No doubt other chronic investigations should be considered.

Further research on cannabis and its various cannabinoids should be entertained because of the lack of consensus on its health hazards. Momentum of investigation should be sustained on account of the current situation of higher potency, greater availability, and use by a lower age group.

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Effects of Marihuana (Cannabis) Smoke on Cellular Biochemistry of In Vitro *Test Systems*

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1. INTRODUCTION

This review, which is concerned with the experimental exploration of the effects of marihuana (cannabis) smoke on cellular metabolism, utilizing *in vitro* systems, is limited to the following topics:

(i) Brief discussion of the chemistry of marihuana smoke, in which only aspects related to cell- and health-damaging components will be considered.

(ii) Effects of marihuana smoke on cell metabolism of *in vitro* test systems. The review will cover only work in which marihuana smoke itself was utilized, and in which cell metabolism after exposure to marihuana smoke was compared with that of nonexposed control cells, and/or with cell metabolism after exposure to placebo marihuana (smoke from which cannabinoids are extracted) or tobacco smoke. Work which deals with effects on cell metabolism of individual components of marihuana such as cannabinoids will not be included.

2. CHEMISTRY OF MARIHUANA SMOKE

During the last two decades, smoking of marihuana cigarettes has become a widespread habit in the Western world, especially among

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young people, including children. In view of the hallucinogenic effects and behavioral alterations observed in heavy marihuana smokers, many clinical and pharmacological studies have been carried out, concerned especially with the psychoactive effects of marihuana smoke and their health and social consequences (see, for example, Tennant, 1974; Paton, 1975; American Medical Association [AMA] Council on Scientific Affairs, 1978). In addition there has been a very large amount of chemical work regarding the naturally occurring constituents of the cannabis plant. An extensive review of the chemical nature of the known naturally occurring constituents of the plant *Cannabis sativa* L. has been published recently by Turner *et al.* (1980). According to these investigations, 421 compounds, belonging to 18 classes, are known to occur in cannabis, with new compounds constantly being discovered and reported. The most extensive chemical work has been done on one class, namely the cannabinoids, and especially on one compound in this class, Δ^9–*trans*-tetrahydrocannabinol (Δ^9–THC). This great interest in Δ^9–THC is understandable because Δ^9–THC is considered to be the compound in cannabis responsible for the psychoactive effects observed in marihuana smokers. The first isolation of Δ^9–THC in its pure form from cannabis was reported by Gaoni and Mechoulam in 1964. This breakthrough stimulated very many chemical, pharmacological and biological studies of Δ^9–THC and other cannabinoids (Mechoulam, 1973; Paton, 1975; Braude and Szara, 1976; Mechoulam *et al.*, 1976; Nahas, 1976; Nahas and Paton, 1979). While there can be no doubt about the great significance of the research on the cannabinoids, not only with respect to their chemical characterization, but also to their biological and in particular their psychoactive properties, this preoccupation with only one group of constituents from marihuana has in some manner retarded chemical and biological research on marihuana smoke itself. In view of the fact that the majority of human marihuana users inhale marihuana smoke, chemical characterization of the smoke itself would appear to be very pertinent for the following reasons:

(i) In addition to up to 15% cannabinoids, marihuana contains a great variety of noncannabinoid compounds among which there are important chemical groups with marked biological activity, such as hydrocarbons, phenols, amino acids, proteins, and sugars (Turner *et al.*, 1980).

(ii) Marihuana smoke is a very complex product, containing hundreds of chemicals, and therefore the chemical and physical nature of fresh marihuana smoke as it is inhaled by the human is completely different from that of individual natural products, such as cannabinoids extracted from the plant or prepared from condensates. This difference between individual components and smoke is the more important because marihuana smoke, like tobacco smoke, consists of two main phases, the particulate and the gas vapor

> phase. Each phase contains a very large number of identified and unidentified constituents, many considered to be contributors to health damage (Leuchtenberger and Leuchtenberger, 1974b; U.S. Department of Health, Education and Welfare [USDHEW], 1979).

Although, as pointed out by Maskarinec *et al.* (1976) "marihuana smoke still remains a poorly defined conglomerate of chemicals," chemical studies carried out within the last five years have revealed similarities between the noncannabinoid health-damaging constituents of marihuana smoke and tobacco smoke. The most important compounds identified so far that are common to both types of smoke and known to have adverse health effects are presented in Table 1. With the exception of nicotine which is present only in tobacco smoke, and the cannabinoids present only in marihuana smoke, it can be seen that the other toxic compounds identified so far in marihuana smoke are the same as those in tobacco smoke. Jones and Foote (1975) and Maskarinec *et al.* (1976) found a great similarity between marihuana and tobacco smokes in regard to their acids, bases and phenols, although Maskarinec *et al.* (1976) reported that marihuana smoke was more complex and contained greater amounts of these constituents than tobacco smoke. Since acids and phenols are considered to play a role in cocarcinogenetic effects of tobacco smoke (USDHEW, 1979), their presence in marihuana smoke is of great interest. Furthermore, recent evidence by Burstein *et al.* (1975) that certain phenols present in marihuana are strong inhibitors of prostaglandin biosynthesis gives additional importance to these noncannabinoid constituents. The finding that polynuclear aromatic hydrocarbons are contained both in tobacco and marihuana smoke deserves special consideration (Adams and Jones, 1973; Brunnemann and Hoffmann, 1976; Lee *et al.*, 1976; Novotny *et al.*, 1976). Lee *et al.* (1976) identified 150 polynuclear aromatic hydrocarbons, many of which are potential carcinogens, in both tobacco and marihuana smoke. Furthermore, the amount of benzopyrene, a known carcinogen, and other pyrenes was found to be significantly higher in marihuana smoke condensate than in tobacco smoke condensate (Lee *et al.*, 1976).

In contrast to the very large amount of analytical chemical research done on components and interaction of the particulate and gas vapor phases of tobacco smoke (USDHEW, 1979), little work has been carried out on marihuana smoke. Therefore, we have little knowledge regarding the interaction of cannabinoids with noncannabinoid constituents of the particulate phase, such as phenols and hydrocarbons, or with constituents of the gas vapor phase, such as HCN, CO, and NO formed during pyrolysis. However, there are already several findings that indicate a discrepancy even between the relative amounts of the cannabinoids in nonpyrolyzed marihuana and in the smoke, of which

TABLE 1

*Common Constituents in Tobacco and Marihuana Cigarette Smoke Judged as Contributors to Health Hazards**

Constituents	Phase Classification Particulate	Gas Vapor	Biological Activity
"Tar"	+		carcinogenic
Phenols	+		cocarcinogenic
Cresols	+		cocarcinogenic
Polynuclear aromatic hydrocarbons	+		tumor initiator and carcinogenic
Nitrogen oxides		+	toxic
Carbon monoxide		+	toxic
Hydrogen cyanide		+	ciliatoxic and toxic
Nitrosamines		+	carcinogenic

* The characterization of the constituents in tobacco smoke as contributors to health hazards is based on the data in reports "Smoking and Health, Report to the Surgeon General of the Public Health Service, U.S. Department of Health, Education and Welfare," 1972, 1979.

only a few will be mentioned here. Mikeŝ and Waser (1971) reported that the ratio of Δ^9–THC to cannabidiol in smoke condensate is different from that in the starting marihuana material. Kinzer *et al.* (1974) found that 50% of Δ^9–THC is destroyed during the smoking process, and Küppers *et al.* (1975) observed that the pharmacological effects of pyrolyzed cannabinoids are different from those of the original material. It would thus appear that an extrapolation of nonpsychoactive data obtained on cells or tissues with a single component of nonpyrolyzed marihuana, such as Δ^9–THC, to the situation existing in cells or tissues exposed to marihuana smoke, is open to criticism. For this reason, information regarding the chemical nature of marihuana smoke itself is urgently needed, to permit assessment of the mechanisms by which inhaled smoke elicits nonpsychoactive toxic effects in humans.

Our lack of knowledge of the chemical composition of marihuana smoke and the urgency of carrying out chemical research in this area, particularly with regard to noncannabinoid constituents of the particulate and gas vapor phases of the smoke, were also stressed in a United Nations report on the chemistry of cannabis smoke (United Nations, Division of Narcotic Drugs, 1975). The necessity for extensive chemical research on marihuana smoke becomes especially evident if one takes into account that tobacco smoke, which does not contain cannabinoids, is considered to play an important etiological role in human lung cancer, cardiovascular disorders, and many other diseases (USDHEW, 1979). In spite of incomplete knowledge, we can say clearly that cannabis smoke not only has a chemical composition similar in many ways to that of tobacco smoke, but in addition contains cannabinoids. Therefore, there is reason to expect that marihuana smoke, besides having adverse psychoactive effects, might have similar and perhaps greater toxic effects than tobacco smoke on the cellular metabolism of the respiratory, cardiovascular, and other systems of the user. Therefore, when experimental attempts are made to explore the nonpsychoactive effects of marihuana on cell metabolism of various tissues, assessment of the influence of marihuana smoke itself would appear especially relevant to the human marihuana smoker.

3. EXPERIMENTAL STUDIES CONCERNED WITH ELUCIDATION OF EFFECTS OF MARIHUANA SMOKE ON CELLS AND THEIR METABOLISM, USING *IN VITRO* TEST SYSTEMS

Compared with the abundance of experimental work in which the influence of Δ^9–THC or other cannabinoids on cells has been studied with *in vitro* test systems (see, for example, volumes edited by Braude

TABLE 2

Cellular Alterations in Cultures of Animal and Human Normal Lung, Normal Animal Testis, and Human Breast Cancer after Short or Prolonged Exposure of Cultures to Fresh Smoke of Marihuana or Tobacco Cigarettes

Species and Type of Tissues		Type of Medium	Time of Exposure in Days		Type of Cigarette Smoke		
animal	human		short-term	pro-longed		Morpho-logy	Mitosis
Mouse lung		E.D.	5		Tobacco + marihuana WS*	+	+
			5		Tobacco WS	(+)	(+)
			—		None	—	—
	Normal adult lung	E.D.	4–10		Marihuana WS	+	+
			4–10		Tobacco WS	(+)	(+)
				45–70	Marihuana WS/GVP**	+++	+++
				45–70	Tobacco WS/GVP	++	++
			—	—	None	—	—
Hamster lung		E.D.		245	Marihuana WS/GVP	+++	++++
				245	Tobacco WS/GVP	++	++
				—	None	—	—

—: no changes, (+): doubtful, +: slight, ++: moderate, +++: marked, ++++: very marked
*WS: whole smoke
**GVP: gas vapor phase

tological and Cytochemical Abnormalities

		Chromosomes			Carcinogenesis		
Proliferation	Cytotoxicity	DNA	Nr.	DNA complement	enhancement	inhibition	References
+	(+)			++			Leuchtenberger and Leuchtenberger, 1971b
(+)	++			(+)			
—	—			—			
+	(+)			+			Leuchtenberger *et al.*, 1973a and b; Leuchtenberger and Leuchtenberger, 1976c
(+)	++			(+)			
+++	+	+++	+++	+++	++		
++	++	++	++	++	+		
—	—	—	—	—	—		
+++ WS* ++++ GVP**	++	++++			+++		Leuchtenberger and Leuchtenberger, 1976c; Leuchtenberger *et al.*, 1976b
++	+++	++			+++		
—	—	—			—		

***E.D.: Eagle Dulbecco
The marihuana (UNC 303) was obtained from Dr. O. Braenden, Director, U.N. Narcotic Laboratory, Geneva, Switzerland.
The tobacco was standard reference tobacco from the University of Kentucky.

TABLE 2 (CONTINUED)

Species and Type of Tissues		Type of Medium	Time of Exposure in Days		Type of Cigarette Smoke		
animal	human		short-term	prolonged		Morphology	Mitosis
Hamster lung		E.D.***		56–730	Marihuana WS/GVP	+++	+++
		Idem + Vit. C or L–cysteine		56–730	Marihuana WS/GVP	(+)	(+)
		E.D.		56–730	Tobacco WS/GVP	++	++
		Idem + Vit. C or L–cysteine		56–730	Tobacco WS/GVP	(+)	(+)
		E.D.		—	None	—	—
		Idem + Vit. C or L–cysteine		—	None	—	—
	Adult lung	E.D.		70–500	Marihuana WS/GVP	+++	+++
		Idem + Vit. C		70–500	Marihuana WS/GVP	++	++
		E.D.		70–500	Tobacco WS/GVP	++	++
		Idem + Vit. C		70–500	Tobacco WS/GVP	+	+
		E.D.		—	None	—	—
		Idem + Vit. C		—	None	—	—
Mouse testis		E.D.	2–6		Marihuana WS		
		E.D.	2–6		Marihuana GVP		
		E.D.	2–6		Tobacco WS		
		E.D.	2–6		Tobacco GVP		
		E.D.	—		None		

Cytological and Cytochemical Abnormalities							
		Chromosomes			Carcinogenesis		
Proliferation	Cytotoxicity	DNA	Nr.	DNA complement	enhancement	inhibition	References
+++	++	+++		+++	++++		Leuchtenberger and Leuchtenberger, 1977b
(+)	(+)	(+)		(+)		++++	
++	+++	++		++	++++		
(+)	(+)	(+)		(+)		++++	
—	—	—		—	—		
—	—	—		—	—		
+++	++	+++	+++	+++	+++		Leuchtenberger *et al.*, 1979
++	(+)				++		
++	+++	++	++	++	++		
+	(+)				+		
—	—	—	—	—	—		
—	—	—	—	—	—		
				+++			Leuchtenberger *et al.*, 1976b
				—			
				—			
				—			
				—			

TABLE 2 (CONTINUED)

Species and Type of Tissues		Type of Medium	Time of Exposure in Days		Type of Cigarette Smoke		
animal	human		short-term	prolonged		Morphology	Mitosis
	Breast cancer SK–Br–3	E.D.		500	Marihuana	+ + +	+ + +
		Idem + Vit. C		500	WS	+ + + +	+ + + +
		E.D.		500	Tobacco	+ +	+ +
		Idem + Vit. C		500	WS	+	+
		E.D.		—	None	+ +	+ +
		Idem + Vit. C		—	None	+	+

ytological and Cytochemical Abnormalities

		Chromosomes			Carcinogenesis		
Proliferation	Cytotoxicity	DNA	Nr.	DNA complement	enhancement	inhibition	References
+ +					+ + +		Leuchtenberger *et al.*, 1979
+ + + +					+ + + +		
+ +					+		
+ + +					—	+ + +	
+					—		
+ + +					—	+ + +	

TABLE 3

In Vitro *Alteration of Cells Obtained from Tissues of Humans or Animals after Inhalation of Marihuana or Tobacco Smoke*

				Cytological				
							Chromosomes	
Species	Tissues and Cells	Inhalation Period in Hours (h), Days (d), Months (m), Years (y)	Type of Cigarette Smoke (n)	Morphology	Mitosis	Proliferation	complement	breakage
Human	Blood lymphocytes	4 y	Marihuana WS† (51)				+	
		—	None (81)				—	
Human ♂, ♀	Blood lymphocytes	chronic > 12 m	Marihuana WS (23)					
		—	None (23)					
Human ♂, ♀	Blood lymphocytes	6 m – 9 y	Marihuana WS (49)				++	++
		—	None (20)				—	—
Human	Blood lymphocytes	chronic > 1 y	Marihuana WS (12)					
		—	None (12)					

*Arylhydrocarbon hydroxylase

†WS: whole smoke ††GVP: gas vapor phase

—: no changes, (+): doubtful, +: slight, ++: moderate, +++: marked ++++: very marked

chemical Abnormalities			Impairment of Immunological Status *in vitro*			
Nucleoprotein DNA	Lipids	Carcinogenesis	Blastogenic response	Rosette formation (T-lymphocytes)	Antibacterial defense	References
++			++	++		Nahas *et al.*, 1974
—			—	—		
				++		Gupta *et al.*, 1974
				—		
						Stenchever *et al.*, 1974
—			—	—		White *et al.*, 1975
—			—	—		

TABLE 3 (CONTINUED)

				Cytologica				
							Chromosomes	
Species	Tissues and Cells	Inhalation Period in Hours (h), Days (d), Months (m), Years (y)	Type of Cigarette Smoke (n)	Morphology	Mitosis	Proliferation	complement	breakage
Human ♂	Blood lymphocytes	2–10 y	Marihuana WS (10)	+	—		++	
		—	None (10)	—	—		—	
Human ♂, ♀	Blood lymphocytes	chronic	Marihuana WS (23)					
		—	None (23)					
Human ♂, ♀	Blood lymphocytes	chronic > 12 m	Marihuana WS (35)					
		—	None (34)					
Human ♂, ♀	Blood lymphocytes	chronic > 3 y	Marihuana WS (22)					
		—	None (15)					
Human	Blood leukocytes and T-lymphocytes	chronic > 1 y	Marihuana WS (13)					
		—	None (8)					
Human ♂, ♀	Blood leukocytes	chronic	Marihuana WS (20)					++
		—	None (20)					—

ochemical Abnormalities			Impairment of Immunological Status *in vitro*			
Nucleoprotein DNA	Lipids	Carcinogenesis	Blastogenic response	Rosette formation T-lymphocytes	Antibacterial defense	References
+						Morishima *et al.*, 1976
—						
				+ +		Cushman *et al.*, 1975
				—		
				+ +		Cushman and Khurana, 1976
				—		
				+ +		Cushman, 1976
				—		
			+ +		+ +	Petersen *et al.*, 1975
			—		—	
						Herha and Obe, 1974

TABLE 3 (CONTINUED)

				Cytological				
							Chromosomes	
Species	Tissues and Cells	Inhalation Period in Hours (h), Days (d), Months (m), Years (y)	Type of Cigarette Smoke (n)	Morphology	Mitosis	Proliferation	complement	breakage
Human ♂	Blood leukocytes	10 y	Marihuana WS (34)	+ + +				
		—	None (18)	—				
Human	Blood lymphocytes	chronic	Marihuana WS† (15)					
		chronic	Tobacco WS (15)					
		—	None (15)					
Rhesus monkey	Blood lymphocytes	3–6 m	Marihuana WS (5)					
		—	None (5)					
Dog ♀	Blood lymphocytes	30 m	Marihuana WS	—	(+)		(+)	
		30 m	Tobacco WS	—	+		(+)	
		—	None	—	(+)		—	
Rat	Spleen cells	5 d	Marihuana WS (10)					
		5 d	Marihuana placebo (10)					
		—	None (10)					

ochemical Abnormalities			Impairment of Immunological Status *in vitro*			
Nucleoprotein DNA	Lipids	Carcinogenesis	Blastogenic response	Rosette formation (T-lymphocytes)	Antibacterial defense	References
+ +						Stefanis and Issidorides, 1976; Issidorides, 1979
—						
	+ + +					Kalofoutis *et al.*, 1978
	—					
	—					
			+ +	+ +		Daul and Heath, 1975
			—	—		
						Genest *et al.*, 1976
				+		Rosenkrantz, 1976
				—		
				—		

TABLE 3 (CONTINUED)

				Cytological				
							Chromosomes	
Species	Tissues and Cells	Inhalation Period in Hours (h), Days (d), Months (m), Years (y)	Type of Cigarette Smoke (n)	Morphology	Mitosis	Proliferation	complement	breakage
Human	Lung alveolar macrophages	Chronic	Marihuana WS (8)	—				
		Chronic	Tobacco WS (8)	+				
		—	None (8)	—				
Rat ♂	Lung alveolar macrophages	h	Marihuana WS					
		h	Marihuana GVP††					
		h	Tobacco WS					
		h	Tobacco GVP					
Rat ♂	Lung alveolar macrophages	3 d	Marihuana WS	+				
		3 d	Marihuana placebo	+				
Rat	Lung alveolar macrophages		Marihuana WS					
			Marihuana GVP					

ochemical Abnormalities			Impairment of Immunological Status *in vitro*			
Nucleoprotein DNA	Lipids	Carcinogenesis	Blastogenic response	Rosette formation (T-lymphocytes)	Antibacterial defense	References
					—	Mann *et al.*, 1970
					—	
					—	
					+ +	McCarthy *et al.*, 1976; Huber *et al.*, 1979
					+ +	
					+ +	
					+ + +	
		+ *				Marcotte *et al.*, 1975
		+ *				
					+	Pereira *et al.*, 1975
					+	

TABLE 3 (CONTINUED)

				Cytological ar				
							Chromosomes	
Species	Tissues and Cells	Inhalation Period in Hours (h), Days (d), Months (m), Years (y)	Type of Cigarette Smoke (n)	Morphology	Mitosis	Proliferation	complement	breakage
Rat ♂	Lung alveolar macrophages and other cells	30 d	Marihuana WS	+				
		30 d	Marihuana GVP	+				
		30 d	Tobacco WS	++				
		30 d	Tobacco GVP	++				
		—	None	—				
Rat ♂	Lung alveolar macrophages	30 d	Marihuana WS					
		30 d	Tobacco					
		—	None					
Rat	Lung alveolar macrophages	h	Marihuana WS					
		h	Marihuana GVP					
		h	Tobacco WS					
		h	Tobacco GVP					
Rat	Lung alveolar macrophages	90 d	Marihuana WS	+++				
		90 d	Marihuana placebo	++				
		90 d	Tobacco WS	++				
		—	None	—				

tochemical Abnormalities			Impairment of Immunological Status *in vitro*			
Nucleoprotein DNA	Lipids	Carcinogenesis	Blastogenic response	Rosette formation (T-lymphocytes)	Antibacterial defense	References
	+ +					Davies *et al.*, 1979
	+ +					
	+ + +					
	+ + +					
	—					
					—	Drath *et al.*, 1979
					—	
					—	
					+ +	Huber *et al.*, 1979a and b
					+ +	
					+ +	
					+ + +	
						Rosenkrantz *et al.*, 1979

TABLE 3 (CONTINUED)

Species (n)	Tissues and Cells	Inhalation Period in Hours (h), Days (d), Months (m), Years (y)	Type of Cigarette Smoke	Cytological an				
							Chromosomes	
				Mor-pho-logy	Mito-sis	Pro-life-ration	comple-ment	break-age
Human ♂	Lung cells	Chronic	Marihuana WS (7)	++		++		
		Chronic	Marihuana and tobacco WS (23)	+++		+++		
		Chronic	Tobacco WS (3)	++		++		
		—	None (3)	—		—		
Human ♂	Cells of oral mucosa	1 y	Marihuana WS (8)	+++				
		—	none (10)	(+)				
Human ♂	Sperm cells	10 y	Marihuana WS (34)	+++				
		—	None (18)	—				
Human ♂	Sperm cells	Chronic and 4 with high doses	Marihuana WS (16)	+++				
Rat	Testis, sperm cells	75 d	Marihuana WS (11)	+++				
		75 d	Marihuana placebo (4)	+				
		—	None (9)	—				

ochemical Abnormalities			Impairment of Immunological Status *in vitro*			
Nucleoprotein DNA	Lipids	Carcinogenesis	Blastogenic response	Rosette formation (T-lymphocytes)	Antibacterial defense	References
		+ +				Tennant *et al.*, 1979
		+ + + +				
		+ +				
		—				
					+ +	Warnock and Shalla, 1975
					(+)	
+ +						Stefanis and Issidorides, 1976
—						
						Hembree *et al.*, 1979
						Huang *et al.*, 1979

and Szara, 1976; Nahas, 1976; Nahas and Paton, 1979), there are few studies concerned with effects on cells of marihuana smoke itself. Lack of research in this area is probably in great part due to inherent difficulties in developing model systems which permit the reproducible exposure of cells or tissues to puffs of fresh smoke (tobacco or marihuana) similar to those inhaled by the human (Leuchtenberger and Leuchtenberger, 1974b).

There have been two main *in vitro* experimental approaches to the study of the effects of marihuana smoke exposure on mammalian cell metabolism:

(i) Studies of cultured mammalian cells derived from normal or abnormal tissues (animal or human) after short or prolonged direct exposure *in vitro* to puffs of fresh smoke from marihuana cigarettes.

(ii) Studies of cells obtained from humans or animals after short or prolonged inhalation *in vivo* of fresh smoke from marihuana cigarettes.

The salient features of these studies, including references, are presented in Tables 2 and 3. Although it is realized that the attempt to present an evaluation of results by positive or negative signs is rather arbitrary and has certain disadvantages, such a presentation may nevertheless facilitate comparison of the data.

Studies of Cultured Mammalian Cells Derived from Normal or Abnormal Tissues (Animal or Human) After Short or Prolonged Direct Exposure *In Vitro* to Puffs of Fresh Smoke from Marihuana Cigarettes

The work started in 1970 by the Leuchtenbergers is the only published systematic experimental investigation of the effects of exposure to fresh marihuana smoke on cultured mammalian cells from lung, testis, breast cancer, and other tissues (Table 2). This work was stimulated by their experimental studies, started in 1956, on the relationship between tobacco smoke and pulmonary carcinogenesis (Leuchtenberger and Leuchtenberger, 1970a and b, 1971a, 1974a and b, 1976a). In their work, they compared effects on cells of smoke from marihuana cigarettes with those of smoke from tobacco cigarettes. Such a comparison appeared necessary not only to obtain a standard of reference for assessing the alterations observed after exposure to marihuana smoke, but also to avoid pitfalls of interpreting results obtained with marihuana smoke as being specific to marihuana smoke alone. The model system developed for this work (Leuchtenberger and Leuchtenberger, 1971a, 1974b, 1976c) permits, under standardized conditions, exposure of mammalian tissue and cell cultures to puffs of fresh smoke from marihuana or tobacco cigarettes. The smoking machine Filtrona CSM12, which simulates human smoking, is particularly suitable for studying the time sequence of alterations at the cell level. Detailed methods of preparation of cigarettes and of cultures, as well as the techniques for exposing the cultures to smoke, have been described previously (Leuchtenberger and Leuchtenberger, 1971b, 1973a and b). After short- or long-term exposure of cultures to smoke, it is possible to follow simultaneous alterations in cellular morphology and growth, and changes in the constituents of cells and chromosomes, such as DNA, RNA, and proteins.

In the cytochemical studies, special attention was focused on DNA metabolism, as examined by autoradiography and special quantitative cytochemical methods, such as Feulgen microspectrography and Feulgen microfluorometry (Leuchtenberger and Leuchtenberger, 1970a). These latter methods are unique for two reasons: first, the DNA content can be determined in a single cell or in part of a cell, such as the nucleus or the chromosomes; and second, the DNA can be studied *in situ* in the original cultures without destroying cell or tissue architecture. Thus, it is possible to compare changes in morphology and DNA directly in the same cell and from cell to cell and to detect changes in DNA before morphological alterations are apparent under the microscope. To determine whether the transformation obtained in cultures was of malignant character, the cultures were injected s.c. into nude mice. Malignancy of tumors observed in nude mice was established by means of histological examination (Leuchtenberger and Leuchtenberger, 1976c; Leuchtenberger *et al.*, 1976b).

Effects of Marihuana Smoke on Lung Cultures

Three main questions were examined:

(i) Does smoke from either tobacco or marihuana cigarettes evoke in cultured lung tissues a sequence of morphological and cytochemical alterations resulting in malignant transformation?

(ii) If a carcinogenic effect does occur, what constituents in the smoke are responsible, and what is their mechanism of action?

(iii) Is it possible to protect the cells against the carcinogenic effect of the smoke?

In an attempt to answer these questions, five different studies were carried out on lung cultures. The salient cytological and cytochemical alterations observed in these studies of animal or human lung cultures after exposure to fresh smoke from marihuana or tobacco cigarettes are presented in Table II. In the first study a comparison was made between the effects on mouse lung explant cultures of short-term exposure to small doses of smoke from tobacco cigarettes and from cigarettes made of the same tobacco but to which marihuana had been added. Adding marihuana to tobacco cigarettes produced a smoke which evoked significantly greater morphological and cytochemical alterations than smoke from cigarettes without marihuana. After receiving small doses of cigarette smoke without marihuana the cells of the cultures closely resembled those in unexposed controls. In contrast, there was an abnormal proliferation of the cells exposed to the same small dose of cigarette smoke with marihuana, accompanied by a significant increase in the mitotic index and by stimulation of DNA synthesis. There were also striking differences in the DNA content. In control cultures and in cultures exposed to tobacco smoke without marihuana, cells with 2 DNA[1] content were 10 and 8 times respectively more common than cells with 4 DNA[2] content. In contrast, in cultures exposed to tobacco smoke with marihuana, the number of cells with 2 DNA decreased, whereas that of cells with 4 DNA content increased significantly. This resulted in a 2 DNA:4 DNA ratio of 2:1 instead of 10:1 or 8:1 (Leuchtenberger and Leuchtenberger, 1971b).

The second type of study consisted of comparing the effects of prolonged exposure to larger doses of smoke from cigarettes made of standard reference tobacco from the University of Kentucky and of smoke from cigarettes made of marihuana only on adult human lung cultures. The sequential alterations observed in human lung cultures were similar after exposure to the marihuana and tobacco smokes. Each type of smoke first evoked inhibition of DNA synthesis and mitosis, followed by abnormalities in cell morphology and mitosis and irregular, abnormal growth. Furthermore, after exposure to each type of smoke, the human lung cultures had an increased number of dividing cells as compared with unexposed cultures. These cells were characterized by a marked variability in number and DNA content of the chromosomes; in other words, there was a disturbance in the genetic equilibrium of the cell population. This derangement was especially pronounced after exposure to smoke from marihuana cigarettes. After exposure to marihuana smoke, there was greater variability in the DNA content of chromosomes, and there appeared to be a greater tendency toward lower DNA content and lower numbers of chromosomes than after smoke from Kentucky standard reference tobacco (Figure 1). The human lung cultures did not survive long enough to provide evidence as to whether the

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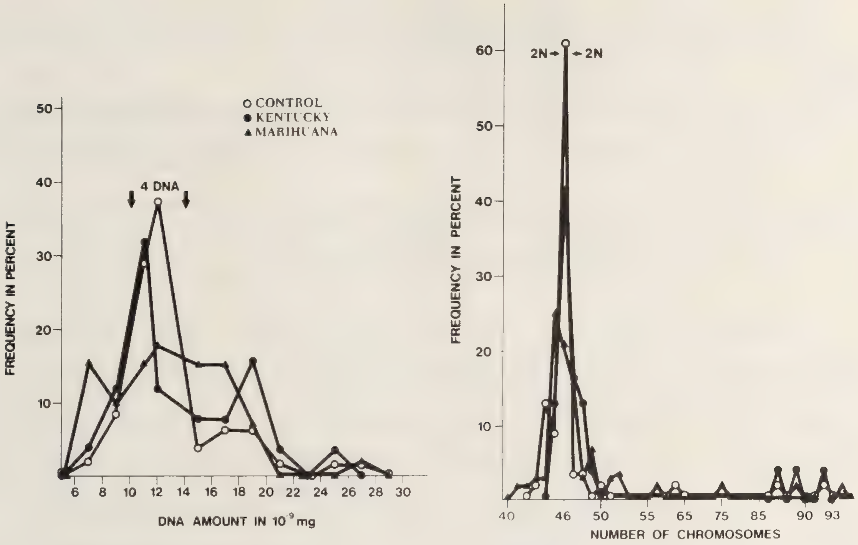
[1] 2 DNA is the amount of DNA in normal diploid somatic mammalian resting cells (i.e., liver, lung, etc.).

[2] 4 DNA is the tetraploid amount of DNA in mammalian somatic cells.

FIGURE 1



Comparison between the DNA content (Feulgen microfluorometry) in telophases and number of chromosomes from control adult human lung explants, and after exposure to fresh smoke from marihuana and Kentucky reference tobacco cigarettes. In the 244 telophases sampled, the DNA content of the tobacco-exposed cells was not significantly different from that of controls ($p > .05$). The DNA content of the marihuana smoke-exposed cells was significantly different from that in the controls ($p = .004$) in that greater percentages had a DNA content between 6–8 x 10^{-9} mg ($p = .025$) and between 14–30 x 10^{-9} mg ($p = .05$), while a lower percentage had the normal amount of 10–12 x 10^{-9} mg. In the 633 metaphases counted, a significantly smaller percentage of cells in the tobacco-exposed ($p = .005$) and in the marihuana-exposed ($p = .0015$) cultures contained the normal 2N complement of chromosomes than did those of controls. The overall distribution of chromosome numbers in the cannabis-exposed cultures was significantly different ($p < .0005$) from that of controls.

atypical changes observed were precancerous changes that would progress to cancer when exposure to smoke was continued for a long period (Leuchtenberger *et al.*, 1973a and b). For this reason, a third study on hamster lung cultures, which have a longer survival time, was carried out (Leuchtenberger *et al.*, 1976b).

In this third type of study, attention was focused on the following questions:

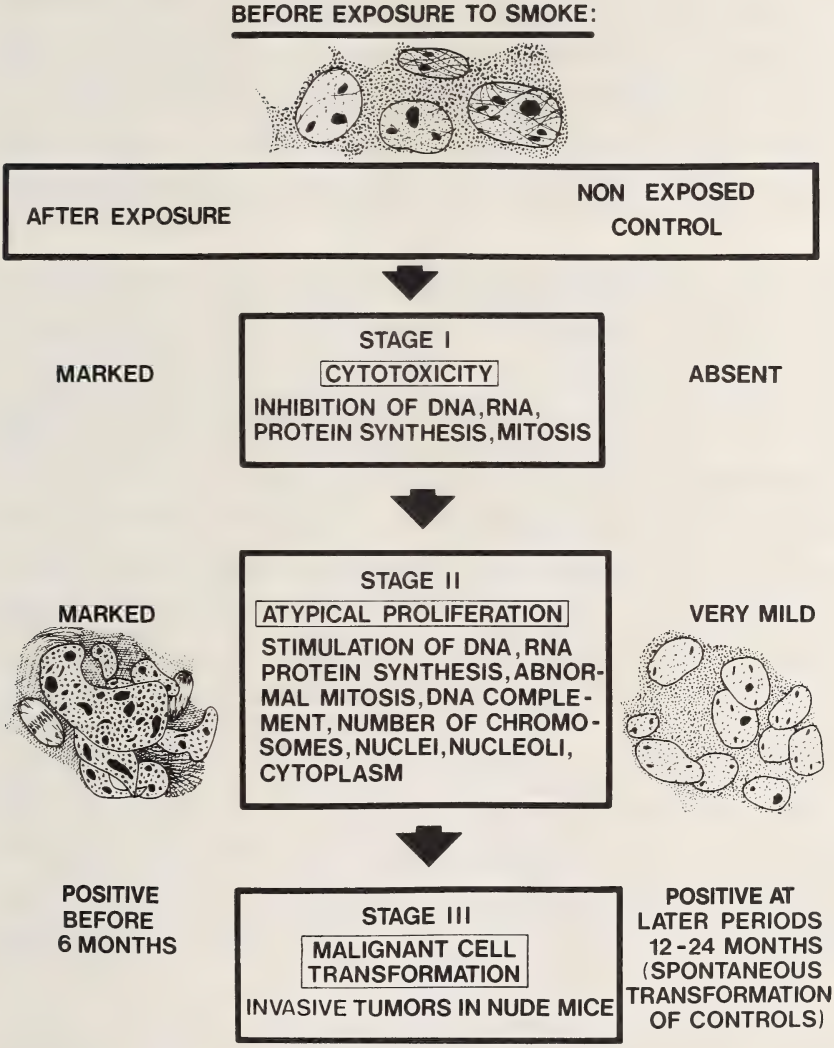
(i) Does continued long-term exposure to fresh smoke from tobacco or marihuana cigarettes evoke sequential alterations that progress to malignant cell transformation?

(ii) Are the changes produced only by whole smoke—i.e., by smoke which contains both the particulate and the gas vapor phase—or can they be caused by the gas vapor phase alone?

The salient features of the sequential changes observed in smoke-exposed and nonexposed hamster lung cultures are presented in Figure 2. The three stages were observed in all exposed cultures, regardless of whether whole tobacco or whole marihuana smoke or only their gas vapor phases were used. However, the cytotoxic effect after marihuana smoke was less than that after tobacco smoke in stage I, which occurred from 1–7 days after the start of chronic exposure. This decreased cytotoxicity may be due to the fact that more smoke from marihuana is lost in the sidestream than smoke from tobacco cigarettes; i.e., less marihuana smoke reached the cultures than tobacco smoke. In spite of this lesser cytotoxicity, proliferative alterations in stage II, occurring within 3–10 wk of the start of exposure to whole smoke or the gas vapor phase, were especially striking in the cultures exposed to marihuana smoke. Furthermore, mitotic abnormalities — such as lagging of chromosomes, presence of pieces of chromosomes in the cytoplasm, enlarged spindles, or variability of DNA content, and rapid abnormal growth — were more marked after exposure to whole marihuana smoke or its gas vapor phase than after exposure to tobacco smoke.

On continued exposure to either type of smoke, the cells gradually lost their epithelial appearance, and the cultures displayed more and more the irregular growth of abnormal fibroblasts with criss-cross formation, and piling up. Stage III, the malignant transformation of the cells, occurred in these cultures within 6 mo of exposure. When 1×10^6 cells of such smoke-exposed cultures were injected into nude mice, fibrosarcomas were observed at the injection site within 10–20 days. At this point, the nonexposed control cultures rarely displayed alterations, and even when more than 1×10^6 cells of the control cultures were injected into nude mice, no fibrosarcomas developed. However, on continued aging, the control cultures underwent alterations similar to those seen in

FIGURE 2


BEFORE EXPOSURE TO SMOKE:
AFTER EXPOSURE
NON EXPOSED CONTROL
STAGE I
CYTOTOXICITY
INHIBITION OF DNA, RNA, PROTEIN SYNTHESIS, MITOSIS
MARKED
ABSENT
STAGE II
ATYPICAL PROLIFERATION
STIMULATION OF DNA, RNA PROTEIN SYNTHESIS, ABNORMAL MITOSIS, DNA COMPLEMENT, NUMBER OF CHROMOSOMES, NUCLEI, NUCLEOLI, CYTOPLASM
MARKED
VERY MILD
STAGE III
MALIGNANT CELL TRANSFORMATION
INVASIVE TUMORS IN NUDE MICE
POSITIVE BEFORE 6 MONTHS
POSITIVE AT LATER PERIODS 12-24 MONTHS (SPONTANEOUS TRANSFORMATION OF CONTROLS)

Time sequential effects of fresh tobacco or marihuana cigarette smoke on hamster lung cells. Originally printed in Marihuana: Chemistry, Biochemistry, and Cellular Effects, *Nahas, G.G. (ed.), Springer-Verlag, New York, 1976.*

stages II and III of the exposed cultures. Between the ages of 12 and 24 mo, a considerable number of the control cultures displayed malignant transformation, producing on injection into nude mice the same fibrosarcomas as were observed after injection of cells from the smoke-exposed cultures (Leuchtenberger and Leuchtenberger, 1976c; Leuchtenberger *et al.*, 1976b). Therefore, smoke from marihuana cigarettes appears to accelerate malignant transformation of cultured lung cells, as does smoke from tobacco cigarettes. The finding that this effect was obtained not only with whole marihuana or tobacco smoke, but also with the gas vapor phase alone, indicates that mainly gas vapor phase constituents were responsible for enhancing malignant transformation.

In the search for a possible identification of the constituents responsible for the carcinogenic effects of cigarette smoke, it was also found that, while the tar content of tobacco smoke was not correlated with the degree of cytotoxicity, the amount of sulfhydryl (SH) reactivity and the NO content of tobacco smoke correlated positively with the capacity of the smoke to enhance atypical growth and malignant transformation of hamster lung cultures (Leuchtenberger and Leuchtenberger, 1974b; Leuchtenberger *et al.*, 1976a and d). To assess the relevance of this concept, a fourth study was carried out to determine whether the hamster lung cultures can be protected against the SH reactivity of marihuana or tobacco smoke by thiols. L-cysteine was chosen because it is known to react with cigarette smoke (Fenner and Braven, 1968; Leuchtenberger and Leuchtenberger, 1974b; Leuchtenberger *et al.*, 1976a), and to afford protection against the potent inhibitory effect of the gas vapor phase of cigarette smoke on the SH enzyme glyceraldehyde-3-phosphate dehydrogenase (Powell and Green, 1972). The effect of vitamin C was also studied, because a decrease in vitamin C level has been found in human cigarette smokers (Pelletier, 1975), and vitamin C has been reported to block NO compounds (Mirvish, 1975) which are known to be present in the gas vapor phase of tobacco smoke. Furthermore, Leuchtenberger and Leuchtenberger (1977a) had found that addition of vitamin C to normal media had a stimulating effect on lysosome formation, and led to a significantly longer survival time of cultures prepared from adult normal lung.

There were significant differences between cultures grown in media with and without the protective agents. Cultures grown without L-cysteine or vitamin C and exposed to fresh smoke from either tobacco or marihuana cigarettes for 1–8 wk, displayed cytotoxic alterations, loss of lysosomes, and marked abnormalities of cell division and of DNA content of chromosomes. In contrast, cultures exposed in the same manner and grown in the same media, but to which L-cysteine or vitamin C was added, showed increase of lysosomes and significantly fewer abnormalities in cell division and DNA content of chromosomes ($p < 0.005$).

Cultures grown without L-cysteine or vitamin C and exposed for 9–24 wk to smoke (whole smoke or gas vapor phase) underwent malignant transformation, while cultures grown in media with L-cysteine or vitamin C and exposed to smoke in the same manner closely resembled those of the nonexposed controls. Cultures which had undergone malignant transformation continued their abnormal growth during the period of observation (over two years). However, when such transformed cultures were grown for three months or longer in media with L-cysteine or vitamin C, the growth became more and more normal and the cultures closely resembled those of the nonexposed controls (Leuchtenberger and Leuchtenberger, 1977b).

These results suggest that, in hamster lung cultures, addition of L-cysteine or vitamin C to media protects against or reverses abnormal growth and malignant transformation occurring either in aged controls (1–2 years old) or in young cultures (3–6 mo old) after repeated exposure to smoke from tobacco or marihuana cigarettes. The increase of lysosomes observed in cultures treated with L-cysteine or vitamin C also points to the possible importance of lysosomes in protecting the cultures against the enhancement of carcinogenesis by smoke, especially since lysosomal damage may be the primary change in carcinogenesis (Allison and Paton, 1965). Although the pathway by which L-cysteine or vitamin C prevented the carcinogenic effects of marihuana or tobacco smoke on hamster lung cells is not known, the possibility should be considered that L-cysteine or vitamin C block the action of carcinogenic or cocarcinogenic gas vapor phase compounds of the smoke, such as NO which is a potential precursor in the formation of N-nitrosamines.

In order to see whether the reduction of abnormalities by L-cysteine or vitamin C was limited to animal lung cultures, a fifth study was carried out in which human adult lung cultures were grown with and without addition of vitamin C. As can be seen from Table 2, vitamin C also reduced cytological and cytochemical abnormalities in human lung cultures after exposure to marihuana or tobacco smoke. However, abnormalities were always more marked after marihuana smoke than after tobacco smoke, regardless of the presence or absence of vitamin C (Leuchtenberger *et al.*, 1979).

Effects of Marihuana Smoke on Testis Cultures

These studies were undertaken primarily to explore the question of whether marihuana or tobacco smoke evoke abnormalities in morphology and in DNA complement of germ cells that are similar to those observed in somatic cells, such as the lung. The effects on mouse testis cultures were compared after short-term exposure to whole smoke from cigarettes made of standard reference tobacco from the University of

Kentucky and from cigarettes made of marihuana only, and to the respective gas vapor phases (Table 2).

In living, as well as in fixed and stained cultures, there were no significant differences in morphology of spermatids between control cultures and those exposed to whole smoke or the gas vapor phase from Kentucky standard cigarettes, or the gas vapor phase of marihuana smoke. However, after exposure to whole smoke from marihuana cigarettes, a considerable number of spermatids had smaller nuclei and showed less staining with basic dyes when compared with spermatids of control cultures and those exposed to the tobacco smoke. There were also no significant differences in the DNA complement of spermatids between control cultures and those exposed to the tobacco smoke, while after marihuana smoke there was a statistically significant increase in frequency of spermatids carrying a DNA complement lower than 1 DNA[3] (Figure 3). This latter observation is in good agreement with results obtained in living mice. Male mice inhaling whole smoke from marihuana cigarettes had a disturbance in spermatogenesis and an increased frequency of spermatids with reduced DNA content (Leuchtenberger *et al.*, 1976b).

Thus, while fresh marihuana smoke has a harmful effect on cultured cells from both the respiratory system and the male reproductive system, different constituents appear to be responsible. The abnormal alterations in the respiratory system appear to be caused mainly by constituents of the gas vapor phase, while alterations in the male germ cells are probably mainly due to constituents in the particulate phase of the marihuana smoke. Since presence of cannabinoids in marihuana smoke can be considered to be the most striking difference in chemical composition between marihuana and tobacco smokes, the cannabinoids may be responsible for the effects of marihuana smoke on male germ cells. Whether they have a direct effect on the DNA or impair meiosis cannot be determined at present. Nevertheless, the low DNA complement in spermatids of cultured mouse testis after exposure to whole marihuana smoke is an alteration that may have serious consequences for genetic information if a sperm derived from a spermatid with low DNA content fertilizes an egg. This finding demands not only similar studies on spermatids of cultured human testis, but also comparative DNA analysis in sperm cells of humans who smoke tobacco and marihuana. Alterations in morphology and number of sperms of human marihuana smokers and of animals inhaling marihuana smoke have been reported by Stefanis

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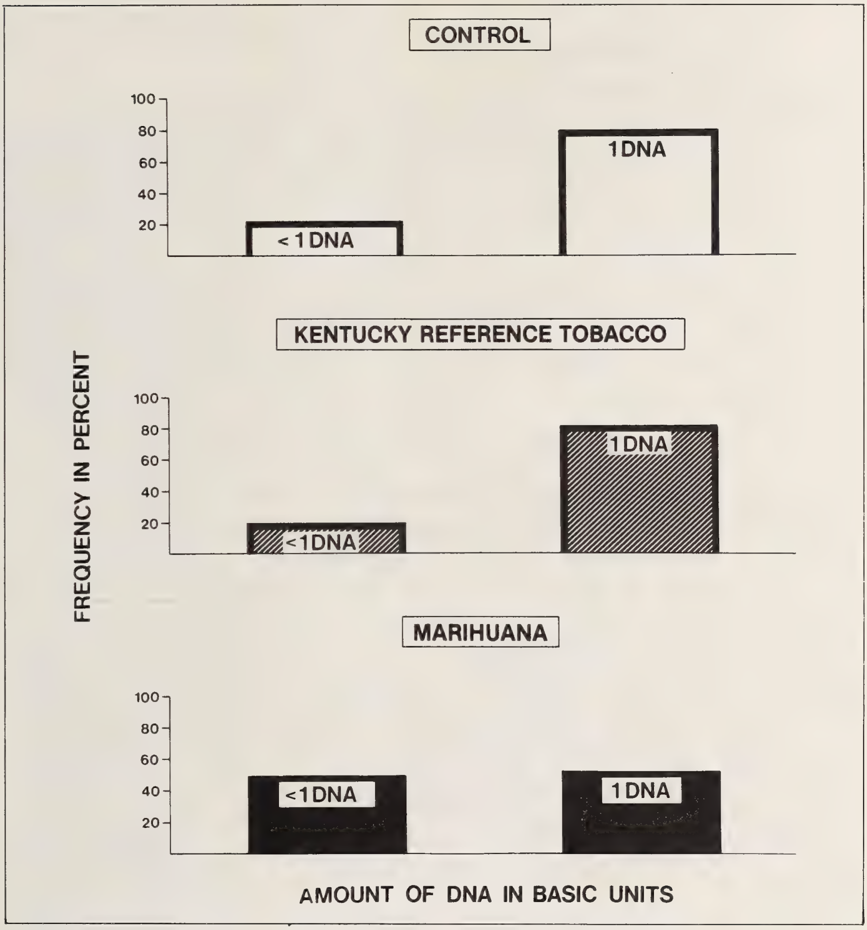
[3] 1 DNA is the amount of DNA in normal haploid mammalian germ cells (i.e., sperm, ova).

FIGURE 3



Comparison between DNA content (microfluorometry) in spermatids from mouse testis explants in control cultures and after exposure to 2–6 puffs daily for 2–6 days of fresh smoke from standard Kentucky reference tobacco and marihuana cigarettes. The figure represents 12 experiments and a total of 1750 spermatids measured. The cultures exposed to Kentucky reference tobacco smoke were not significantly different from control cultures. The marihuana smoke-exposed cultures were significantly different from both control and tobacco-exposed cultures ($p << .000001$).

and Issidorides (1976), Hembree *et al.* (1979), Huang *et al.* (1979), and Issidorides (1979) (Table 3).

Effects of Marihuana Smoke on Human Breast Cancer Cultures

This study was undertaken to determine whether the higher frequency of abnormalities in cells of normal human tissue cultures could also be observed in cancerous tissue cultures after exposure to marihuana smoke. Since previous studies disclosed that vitamin C tended to promote cell differentiation in cultures of a human breast cancer (SK–Br–3) (Leuchtenberger *et al.*, 1979), the breast cancer cultures were grown in the absence or presence of vitamin C and exposed to marihuana or tobacco smoke (Table 2). Breast cancer cultures grown in Eagle Dulbecco medium without vitamin C and exposed to either marihuana or tobacco smoke showed an increase of growth rate and mitotic abnormalities, the frequencies of both features being significantly greater after marihuana than after tobacco smoke. The greatest difference between tobacco and marihuana smoke was noted in breast cancer cultures grown in the presence of vitamin C. While vitamin C led to a statistically significant decrease of mitotic abnormalities in nonexposed and tobacco smoke-exposed cultures, it did not do so in cultures exposed to marihuana smoke. Furthermore, within a period of 5–7 mo, vitamin C in nonexposed and tobacco smoke-exposed cultures also led to a gradual disappearance of the large cancer cells and to the occurrence of pseudoglandular structures. This tendency to differentiation of the cancer cultures was not observed after marihuana smoke, even when grown for 18 mo in the presence of vitamin C. After marihuana smoke exposure, vitamin C actually appeared to have an opposite effect. Cultures showed an increasingly accelerated growth of large atypical cells, accompanied by the occurrence of abnormally large mitotic figures, especially of tripolar spindles. The frequency of tripolar spindles in breast cancer cultures exposed to marihuana smoke was seven times as large in those grown with vitamin C as in those grown in its absence (22% against 3.2%, $p < 0.0005$).

It therefore appears that exposure of human lung and breast cancer cultures to fresh smoke from marihuana cigarettes not only evokes a significantly higher degree of mitotic abnormalities than tobacco smoke, but also alters the response of breast cancer cultures to vitamin C and evokes a further dedifferentiation of the breast cancer cells. In other words, it would seem that marihuana smoke alters the metabolism of the cells in such a manner that a naturally occurring and essential co-factor, such as vitamin C, is utilized as a promoter of abnormal growth. The pathway by which vitamin C exerts its regulatory effect on growth in nonexposed or tobacco smoke-exposed breast cancer cultures is unknown. However, the modification of this pathway induced by marihuana smoke indicates a fundamental metabolic change (Leuchtenberger *et al.*, 1979).

The results obtained on human cancer cultures support the concept that smoke from marihuana cigarettes interferes significantly more with cell metabolism than does tobacco smoke (Leuchtenberger *et al.*, 1973a and b; Leuchtenberger and Leuchtenberger, 1976c). The finding that this difference was observed not only in normal cells, but also in cancer cells, and that cancer cells exposed to marihuana smoke showed an opposite response to vitamin C compared with that of nonexposed cells or of those exposed to tobacco smoke, deserves special attention. It might provide valuable clues to the mechanisms of action of both marihuana smoke and vitamin C in relation to regulation of cell growth and differentiation.

In Vitro *Studies of Cells Obtained from Humans or Animals after Short or Prolonged Inhalation of Fresh Smoke from Marihuana Cigarettes*

In vitro studies of cells derived from human smokers are a particularly good experimental model for assessing the effects of marihuana smoke on cell metabolism because of their direct relevance to the human marihuana problem. However, for ethical reasons it is out of the question to take indiscriminately tissue biopsies for cell studies from human marihuana smokers. Thus examination of metabolism in cells derived from human marihuana smokers is of necessity limited to a few specimens, such as blood or other body fluids, or to desquamated cells from the oral mucosa. For this reason, most of the studies of other types of cells have to be carried out on tissues from animals which have inhaled smoke. Although it is possible with the use of a smoking machine to produce puffs of smoke that are as similar as possible to those inhaled by human smokers (Leuchtenberger and Leuchtenberger, 1974a), one has to take into account a fundamental difference between human and animal smokers of marihuana. The human inhales the smoke actively and voluntarily by breathing through the mouth, while animals, particularly rodents such as rats or mice, inhale the smoke involuntarily and mainly by nose breathing.

The influence of marihuana smoke has been studied on five different types of cells obtained from humans or animals, namely blood lymphocytes, alveolar macrophages, lung epithelium, oral mucosa, and sperm cells. The salient features observed in such cells are presented in Table 3.

Effects on Blood Lymphocytes

Two main questions were examined:

(i) Does prolonged inhalation of marihuana smoke *in vivo* alter the immunological properties of the T–lymphocytes studied *in vitro*?
(ii) Does prolonged inhalation of marihuana smoke affect mitosis, nucleoprotein or DNA synthesis, and chromosomal structures or complement?

Comparative immunological studies *in vitro* were carried out on lymphocytes from nonsmokers and from chronic human marihuana smokers (with a history of use ranging from 1–10 yr) by different investigators. All investigators (Gupta *et al.*, 1974; Nahas *et al.*, 1974; Cushman *et al.*, 1975; Petersen *et al.*, 1975; Cushman, 1976; Cushman and Khurana, 1976) except White *et al.* (1975) observed a significant reduction of rosette formation by T–lymphocytes and/or reduction of the blastogenic response. A significant increase in lipid and phospholipid concentrations has also been reported (Kalofoutis *et al.*, 1978). All of these findings are accepted as indications of an impairment of the immunological status *in vitro*. Furthermore, some investigators also noted inhibition of nucleoprotein or DNA synthesis, reduction of chromosomal complement, and abnormalities of chromosomes in the lymphocytes (Herha and Obe, 1974; Nahas *et al.*, 1974; Stenchever *et al.*, 1974; Morishima *et al.*, 1976; Stefanis and Issidorides, 1976). Reduction of immunological status was also noted in monkeys after exposure to inhalation of marihuana smoke for 3–6 mo (Daul and Heath, 1975) and in rats exposed to inhalation of marihuana smoke for 5 days (Rosenkrantz, 1976), while rats exposed to placebo marihuana smoke did not show this reduction. However, Genest *et al.* (1976), who examined lymphocytes obtained from dogs after 30 mo of inhalation of marihuana or tobacco smoke, did not find any significant alterations in cell division or chromosomal constitution. Based on data obtained on lymphocytes by the majority of investigators, it would appear that inhalation of marihuana smoke interferes with the immunological properties of lymphocytes *in vitro*, and with their nucleoprotein metabolism and chromosomal status. Since reduction of immunological properties or inhibition of nucleoprotein synthesis and chromosomal damage have also been noted in cultured lymphocytes exposed to Δ^9–THC or other cannabinoids (Morishima *et al.*, 1976; Nahas, 1976; Nahas and Paton, 1979), it has been concluded that the impairment of immunological status or of nucleoprotein synthesis in marihuana smokers is due to cannabinoids in the marihuana smoke. However, since impairment of immunological status has been observed in mice (see, for example, Leuchtenberger and Leuchtenberger, 1974a), and in humans after tobacco cigarette smoke (U.S. Senate, 1974), the interpretation that cannabinoids are solely responsible for the immunological impairment observed in the human marihuana smoker is not justified. Indeed, reduction of the immunological status in mice occurred also after inhalation of the gas vapor phase of tobacco smoke (Leuchtenberger and Leuchtenberger, 1974a), which obviously contains no cannabinoids.

Effects on Alveolar Macrophages and Epithelium of the Lung

Three main questions were examined:

(i) Does inhalation of marihuana smoke alter morphology, metabolism, and/or the antibacterial defense capability of the alveolar macrophages?

(ii) If there is an impairment of the alveolar macrophages, are the factors responsible found in the particulate phase, or in the gas vapor phase of the marihuana smoke?

(iii) Does inhalation of marihuana smoke elicit alterations of cells of the respiratory tract that indicate enhancement of pulmonary carcinogenesis?

In order to answer the first two questions, with the exception of Mann *et al.* (1970) who studied human marihuana smokers, all investigators (Marcotte *et al.*, 1975; Pereira, 1975; Davies *et al.*, 1979; Huber *et al.*, 1979a and b) examined alveolar macrophages of rats after exposure to inhalation of marihuana smoke (whole smoke or gas vapor phase), cannabinoid-free placebo marihuana smoke, or tobacco smoke (whole smoke or gas vapor phase). Mann *et al.* (1970) who obtained cells by bronchopulmonary lavage from human lungs, did not find any significant differences between the ability of the macrophages from nonsmokers, tobacco smokers, and marihuana smokers to ingest heat-killed *Candida albicans.* Antibacterial defense capability of rat alveolar macrophages was assessed *in vitro* after relatively short periods of *in vivo* inhalation of the smoke, varying from several hours to daily for a maximum of 30 days. Although Drath *et al.* (1979) did not find significant alterations after 30 days of daily inhalation of either marihuana or tobacco smoke, Marcotte *et al.* (1975), Pereira *et al.* (1975), Davies *et al.* (1979), and Huber *et al.* (1979a and b) observed either impairment of antibacterial defense, alterations in morphology, or changes in lipids. The finding that the gas vapor phase of either marihuana or tobacco smoke elicited essentially the same alterations as did the whole smoke (McCarthy *et al.*, 1976) indicates again that the cannabinoids were not solely responsible for the changed behavior of the rat macrophages observed after inhalation of marihuana smoke. In this connection, the report published by Marcotte *et al.* (1975) is of special interest. Their study showed that the effects on alveolar macrophages of placebo cannabinoid-free marihuana smoke and of marihuana smoke were essentially the same.

The third question as to whether chronic inhalation of marihuana smoke evoked cellular abnormalities in the respiratory system, indicative of enhancement of pulmonary carcinogenesis, was studied in human hashish smokers by Tennant (1974) and Tennant *et al.* (1979). Examining 23 young American soldiers (ages 17–36 yr) who were hashish and tobacco cigarette smokers, they found not only chronic bronchitis in all of them, but also cellular abnormalities indicating precarcinogenic alterations "associated with cancer of the lung" that were revealed on microscopical examination of lung biopsies. Such lesions are usually observed in much older men who have been heavy tobacco cigarette smokers for many years. While there were no changes in nonsmokers, some of those who smoked either only hashish or only tobacco cigarettes had similar lesions, but to a lesser degree. It thus would appear that tobacco plus hashish smoking by young people significantly enhances the risk of human pulmonary carcinogenesis, not only when compared with nonsmoking but also with the smoking of only tobacco or only hashish.

Effects on Cells of the Oral Mucosa

The studies by Warnock and Shalla (1975) on cellular aspects of the human oral mucosa after marihuana smoking deserve consideration, not only in connection with the decreased antibacterial defense mechanisms of alveolar macrophages, but also in connection with the findings of Tennant (1974) and Tennant *et al.* (1979). On comparison of the oral epithelium of eight nontobacco-smoking males, aged 21–35 yr, who had smoked marihuana cigarettes for one year, with 10 nonsmoking controls, significantly higher frequencies of degenerative cells, bacteria and leukocytes were noted in the oral tissue of the marihuana smokers than of the nonsmokers. The possibility has to be considered that inflammatory and/or infectious processes of the oral epithelium may be one of the early steps in the impairment of alveolar antibacterial defenses, development of bronchitis, and pulmonary carcinogenesis observed in marihuana smokers (Tennant, 1974; Tennant *et al.*, 1979).

Effects on Sperm Cells

Four different studies were carried out to assess effects of cannabis smoking on sperm cells, three on human smokers (Stefanis and Issidorides, 1976; Hembree *et al.*, 1979; Issidorides, 1979) and one on rats (Huang *et al.*, 1979). Hembree *et al.* (1979) observed that in 12 of 16 chronic marihuana smokers, after four weeks smoking of 8–20 marihuana cigarettes per day, there was a significant decline of sperm count and of the percentage of sperms with normal morphology. Stefanis and Issidorides (1976) did not find an altered morphology in the sperm heads of 34 chronic hashish smokers. However they reported, on the basis of cytochemical studies, a diminution of arginine-rich proteins within the sperm nucleus. A later ultrastructural study by Issidorides (1979) on 47 chronic hashish smokers and 40 matched controls revealed that there were marked morphological alterations in the acrosomes of the sperm heads of the hashish smokers. Issidorides advanced the hypothesis that the abnormalities in the acrosomes of the sperm heads may be interlinked with the previously observed depletion of arginine in sperms of hashish smokers (Stefanis and Issidorides, 1976). Huang *et al.* (1979), examining rats after inhalation of marihuana smoke for 30 consecutive days, noted not only a decreased sperm count, but also, in sperms taken from the cauda epididymis, a high frequency of altered morphology, such as dissociated heads and tails. Placebo cannabinoid-free marihuana smoke had similar effects; however, the alterations were less marked than after marihuana smoke.

It thus would appear that inhalation of marihuana smoke by humans or by animals affects the morphology and protein metabolism of sperm cells. The lesser but still appreciable activity of placebo marihuana smoke on sperm morphology indicates that in addition to cannabinoids, noncannabinoid components of the smoke may also play a role in evoking the abnormalities.

4. SUMMARY AND CONCLUSIONS

Marihuana smoke is a very complex product consisting of a particulate and a gas vapor phase. It contains, in addition to the cannabinoids, hundreds of identified and unidentified noncannabinoid constituents. The cannabinoids, especially Δ^9–THC, are very important because of their psychoactive effects observed in marihuana smokers. Some of the identified noncannabinoid components in marihuana smoke are the same as those in tobacco smoke, such as phenols and polynuclear aromatic hydrocarbons, but occur often in higher concentration, and are known to play an important role in carcinogenesis. A very large amount of work has been done on chemistry and biosynthesis of cannabinoids, particularly in regard to their psychoactive effects. In contrast, little chemical research has been carried out on the noncannabinoid smoke constituents and their interaction with cannabinoids during pyrolysis. The necessity of more work in this area is clear because of the established similarity between marihuana and tobacco smoke, the latter known to play an important etiological role in human lung cancer, cardiovascular lesions, and a wide spectrum of other human diseases.

Marihuana smoke (whole smoke or gas vapor phase) evoked in cultured lung cells essentially the same sequence of alterations in metabolism as did tobacco smoke, such as abnormalities in mitosis, DNA complement, chromosomal number, proliferation, and enhancement of malignant transformation. The alterations in human lung cells, particularly those of mitosis, DNA and chromosomal number, were more marked after exposure to marihuana smoke than after tobacco smoke. Marihuana smoke evoked in human breast cancer cultures a significantly higher frequency of mitotic abnormalities than did tobacco smoke, regardless of whether the cultures were grown in the absence or presence of vitamin C. The response to vitamin C of marihuana smoke-exposed breast cancer cultures was completely different from that of tobacco-exposed ones. While vitamin C caused a reduction of mitotic abnormalities in tobacco-exposed cultures and led to differentiation, it accelerated not only the abnormal growth, but also the dedifferentiation of the breast cancer cells in marihuana smoke-exposed cultures. Whole marihuana smoke evoked a decrease in DNA content in spermatids of cultured animal testis. This alteration was not found in spermatids after exposure to the gas vapor phase of marihuana smoke, or after exposure to tobacco smoke (whole smoke or the gas vapor phase).

The cell studies on cultured human lung and human breast cancer indicate not only that noncannabinoid and cannabinoid components of marihuana smoke are involved in the enhancement of malignant transformation, but also suggest strongly that the cannabinoids interfere with the vitamin C-related metabolism of breast cancer cells. The cell studies on cultured animal male germ cells indicate that mainly the cannabinoids of marihuana smoke were responsible for the alterations in DNA.

T-lymphocytes obtained from either human marihuana smokers or from animals after inhalation of marihuana smoke, demonstrated reduced *in vitro* immunological responsiveness, inhibition of DNA synthesis and chromosomal damage. Impairment of the antibacterial defenses of alveolar macrophages was also observed after cannabinoid-free marihuana smoke, the gas vapor phase of marihuana smoke, or after tobacco smoke (whole smoke or gas vapor phase). These findings indicate that noncannabinoid components of marihuana smoke are mainly involved. Cells from oral mucosa obtained from human marihuana smokers revealed cell degeneration, many leuckocytes, and an increased frequency of bacteria, i.e., alterations which might be interpreted as a decreased resistance to bacterial infections.

Lung biopsies from young male human smokers of both hashish and tobacco showed precancerous lesions of cells observed usually only in much older men who smoked tobacco heavily for many years. These data suggest the marked enhancement of pulmonary carcinogenesis by cannabis smoke.

Sperm obtained from human marihuana smokers or from animals after inhalation of marihuana smoke demonstrated abnormalities in morphology and/or in nucleoproteins.

The information obtained so far from chemical analysis of marihuana smoke, and from *in vitro* and *in vivo* studies of the effects of the noncannabinoid components of marihuana smoke on cell metabolism, discloses not only a similarity between the noncannabinoid constituents of marihuana and tobacco smoke, but supports the concept that smoking of marihuana might even be a greater hazard to human health than smoking of tobacco. Marihuana smoke not only reduced the *in vitro* immunological status of T-cells, and enhanced abnormalities of DNA metabolism and pulmonary carcinogenesis more than tobacco smoke, but had an adverse effect on male germ cells that was not observed after exposure to tobacco smoke.

No extrapolation of the experimental results obtained on cultured cells to cell metabolism of human marihuana smokers is possible. Nevertheless the relevance of these experimental data to the human problem is indicated by their correlation with chemical data and the parallelism of alterations in cell cultures after exposure to marihuana smoke with those observed in human marihuana smokers, such as enhancement of pulmonary carcinogenesis, and impairment of spermatogenesis. More correlated chemical and biological studies of the effects of marihuana smoke on cell metabolism are very much needed for the further elucidation of the health hazards of marihuana smoking.

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Interaction of Cannabis with Arginine Metabolism Underlies Biological Effects: A New Hypothesis on Mechanism of Action

MARIETTA R. ISSIDORIDES, PhD

1. INTRODUCTION

In biological research, the effort to reconcile paradoxical data has often precipitated a better understanding of hitherto unclear findings and, at times, uncovered relationships between conflicting but reproducible results. Such an effort with respect to data obtained from cellular studies of chronic hashish users resulted in the formulation of the hypothesis that cannabis may act through a common metabolic denominator, namely arginine depletion (Issidorides, 1979). The initial data from the cellular studies clearly indicated similar repercussions of cannabis on arginine metabolic pathways in two cell populations as functionally diverse as peripheral leukocytes and ejaculated spermatozoa.

Specifically, the light and electron cytochemical method used for the detection of arginine-rich proteins (MacRae and Meetz, 1970) showed a reduction of arginine-rich histones in most of the nuclei of both cell types (Stefanis and Issidorides, 1976). This reduction seemed counterbalanced by increased amounts of lysine-rich histones. The altered histone ratio in the lymphocytes denoted over-differentiation, i.e., over-repression of the genome (Littau *et al.*, 1965), a state consistent with a reduced potential to respond to antigenic stimuli (Black and Ansley, 1965, 1966). In the spermatozoa, however, the similarly altered histone ratio denoted an arrest of maturation and of final differentiation

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(Vaughn, 1966; Coelingh *et al.*, 1969; Calvin and Bedford, 1971; Silvestroni *et al.*, 1976). It is amply documented that differentiation of the sperm nucleus entails a change in protein synthesis, whereby lysine-rich somatic histones are gradually depleted and replaced by arginine-rich protamines (Vaughn, 1966; Gledhill *et al.*, 1966; Fawcett *et al.*, 1971). The latter insolubilize DNA and pack it into the small nuclear space in a highly condensed, inert state (Kawashima and Ando, 1978). The subsequent data from studies of chromatin ultrastructure in chronic hashish users (Issidorides, 1979) indicated that the effects of cannabis were conflicting, i.e., over-condensed leukocyte nuclei and decondensed sperm nuclei. The information that in somatic cells chromatin condensation can be induced by arginine-poor media (Aula and Nichols, 1967; Weissfeld and Rouse, 1977) offered the clue that resolved the paradox of opposite chromatin condensations. Actually, the same mechanism of action observed in both leukocytes and sperm, i.e., arginine depletion, was sufficient to explain the opposite repercussions of cannabis on the condensation of their chromatin (Issidorides, 1979).

That alterations in a single biochemical pathway may lead to a variety of effects on cellular processes is no novel concept: "the reactions leading to cAMP formation and the processes depending upon the activity of the membrane-bound ATPase systems are illustrations of this point" (Toro-Goyco *et al.*, 1979). What, perhaps, is novel is the concept that cannabis may cause its multiple biological effects by interfering with arginine in its multiple and fundamental actions in biological systems. The present report examines the hypothesis of cannabis/arginine interactions. To this end, additional findings from blood and sperm of chronic hashish users, i.e., the subjects of our previous investigations, will be reported and discussed.

2. NEW CELLULAR DATA FROM CHRONIC HASHISH USERS

The findings derive from the group of 34 hashish users and 18 male controls recruited from the original larger population that was extensively studied in a long-term controlled investigation of chronic cannabis use in man (Stefanis *et al.*, 1977).

Data regarding the clinical material have appeared in detail elsewhere (Stefanis and Issidorides, 1976). Data regarding hashish use of this group are shown in Table 1. The material smoked by the subjects contained 4%–5% Δ^9–THC (THC) and was classified as of average strength. The electron microscopic methods used, i.e., PTAH-block-staining for chromatin condensation and the ammoniacal silver (AS) reaction for electron cytochemistry of arginine-rich proteins, are dis-

TABLE 1

Data of Hashish Use

	Starting age (years)	Years of use	Past use		Current use	
			Times/day	Daily quant.*	Times/day	Daily quant.*
Mean	16.3	25.1	6	8.2 g	2.2	3.2 g

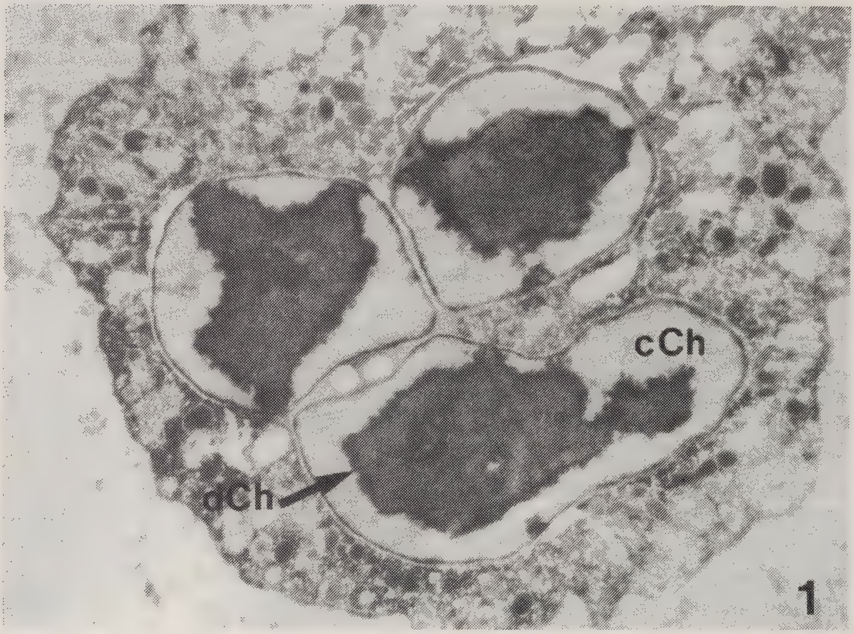
*Estimated

cussed in detail elsewhere (MacRae and Meetz, 1970; Issidorides *et al.*, 1975; Stefanis and Issidorides, 1976; Issidorides and Katsorchis, 1981).

Ultrastructure of Somatic Nuclei

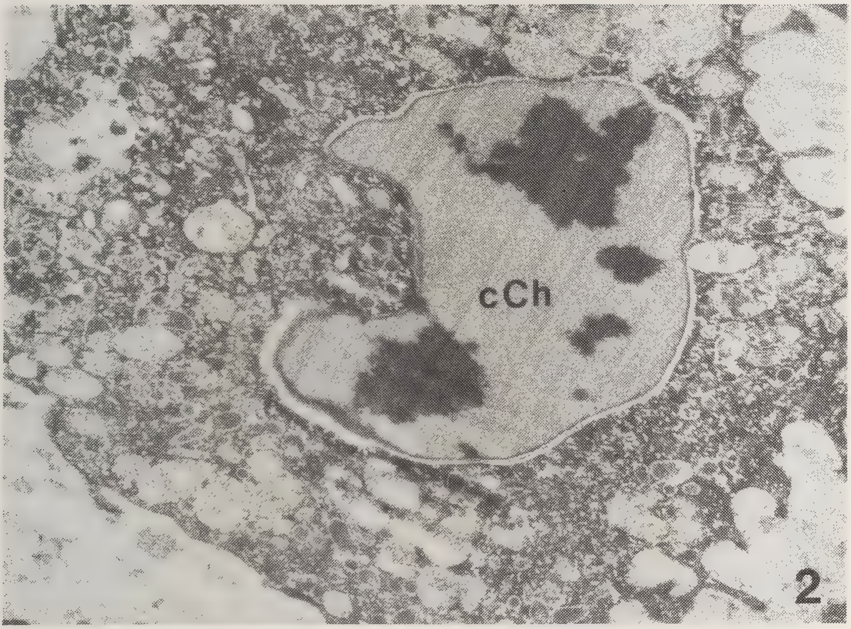
The high sensitivity of the PTAH-block-staining method for differentiating dispersed chromatin as electron-dense while leaving condensed chromatin electron-lucent (Figure 1) was used to advantage for the demonstration of the increased amounts of inert condensed chromatin in the neutrophils of the users (Figure 2). Furthermore, this method established that nuclear projections of condensed chromatin, the "drumsticks," are encountered with high frequency in the thin sections of leukocyte pellets (Figures 3 and 4). This fact corroborates the high percentage of occurrence of this marker of female blood phenotype (Davidson and Smith, 1954) noted earlier in routine Giemsa smears of the blood of users (Stefanis and Issidorides, 1976). Many granulocytes of the users also displayed spherical bodies of condensed chromatin, unattached to the nucleus (Figures 4 and 5), which usually result from abnormal reconstitution of the nucleus after the last division in the bone marrow (Bessis, 1973). Similar pieces of chromosomes isolated from the nucleus were observed in hamster lung cultures exposed to marihuana smoke (Leuchtenberger *et al.*, 1976).

FIGURE 1



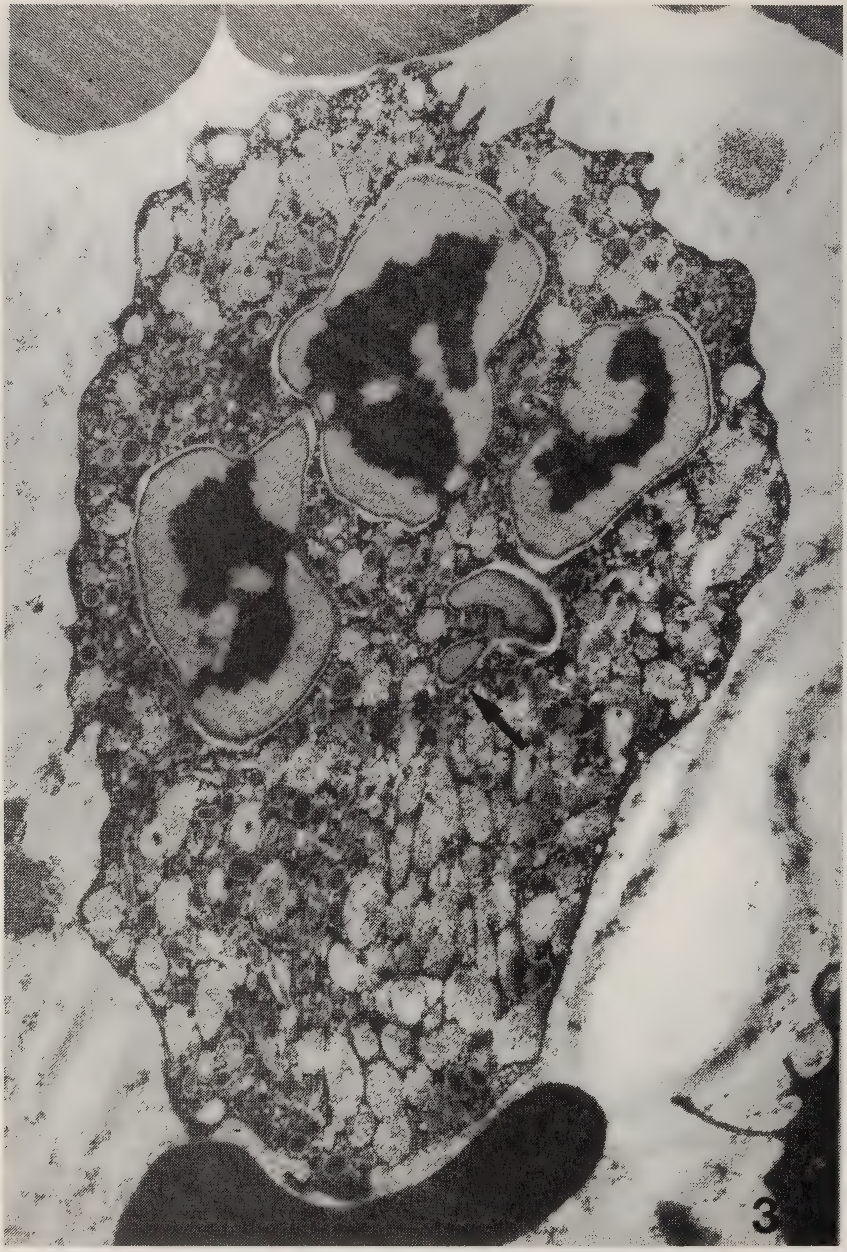
Electronmicrograph of neutrophil from control showing 3 nuclear lobes. Note electron-lucent condensed chromatin (cCh) and thin layer of electron-dense dispersed chromatin (dCh) at the border of the nucleoplasm. Glutaraldehyde/$KMnO_4$ *fixation, PTAH-block-staining.*

FIGURE 2



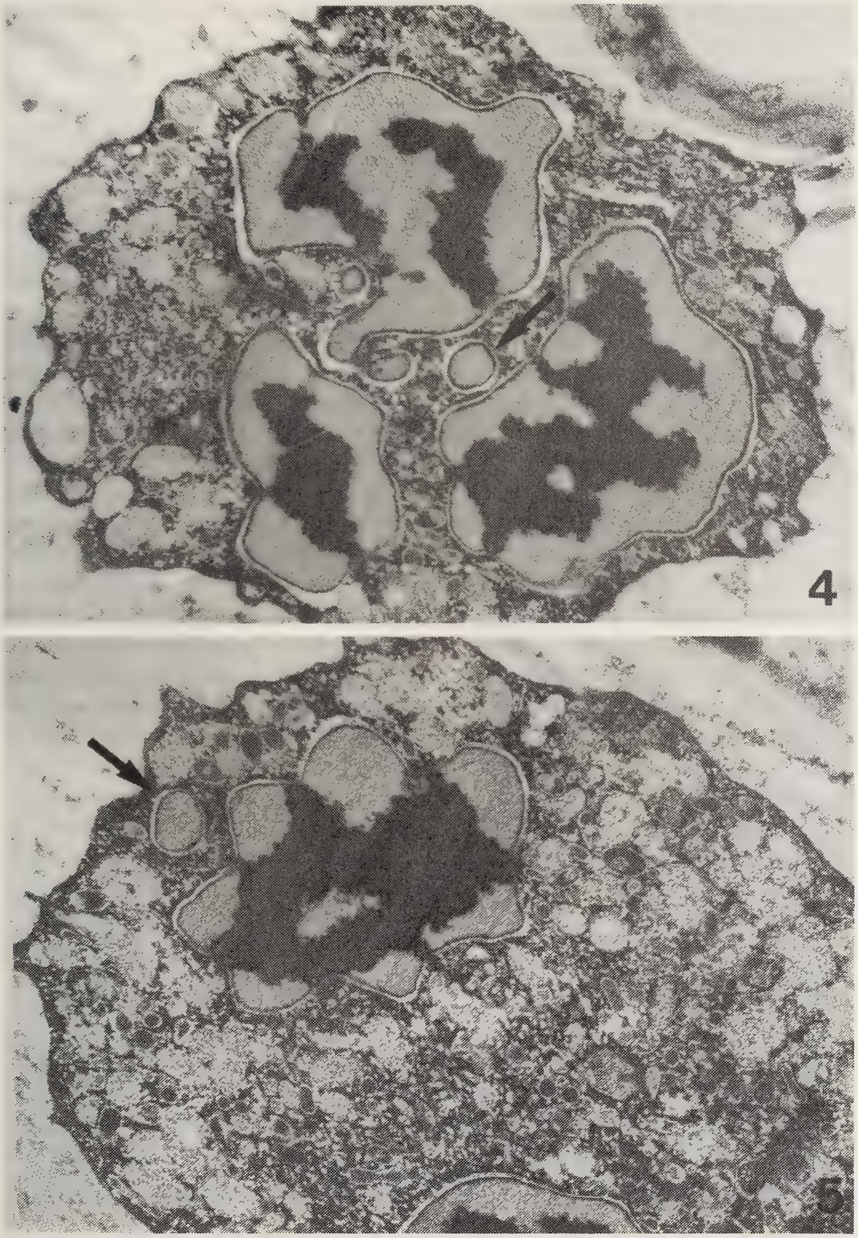
Electronmicrograph of neutrophil from chronic hashish user. Note nuclear lobe with increased mass of condensed chromatin (cCh). Glutaraldehyde/$KMnO_4$ *fixation, PTAH-block-staining.*

FIGURE 3



Electronmicrograph of neutrophil from chronic hashish user showing "drumstick" nuclear projection of condensed chromatin (arrow). Glutaraldehyde/$KMnO_4$ fixation, PTAH-block-staining.

FIGURES 4 and 5



Electronmicrographs of neutrophils from chronic hashish users showing spherical masses of condensed chromatin (arrows) unattached to nucleus. Glutaraldehyde/$KMnO_4$ fixation, PTAH-block-staining.

Various reports have shown that, in the absence of arginine, morphological disorganization of nuclei and fragmentation of chromosomes take place in cultured dividing cells, while in resting cells the deficiency is expressed as an increase in chromatin condensation (Freed and Schatz, 1969). Furthermore, the changes induced by arginine deficiency affecting the organization of nucleoproteins are reversible upon restoration of arginine to the medium; they are the consequence of faulty histone metabolism and, hence, abnormal chromatin configuration (Weissfeld and Rouse, 1977). The importance of arginine in the culture medium for the maintenance of normal nuclear morphology was also shown in a different experimental design. When a highly purified preparation of arginase was added to the culture medium of embryonic fibroblasts, it caused rapid pyknosis of the nuclei in the resting cells and clumping of metaphases in the dividing ones (Bach and Simon-Reuss, 1953). It was concluded that, since arginase does not penetrate the cells, the observed effects were solely due to enzymic attack directed against arginine in the medium.

On the basis of these experiments, our findings on postmitotic neutrophils of chronic hashish users, as well as the findings of Leuchtenberger and collaborators (1976) on dividing cultures exposed to cannabis, are compatible with a possible depletion of arginine under the influence of the drug in the plasma and the culture medium respectively. The far-reaching repercussions of such a depletion of arginine on cell structure and function will become apparent in the review of the experimental results obtained by other workers, which appears later in this text.

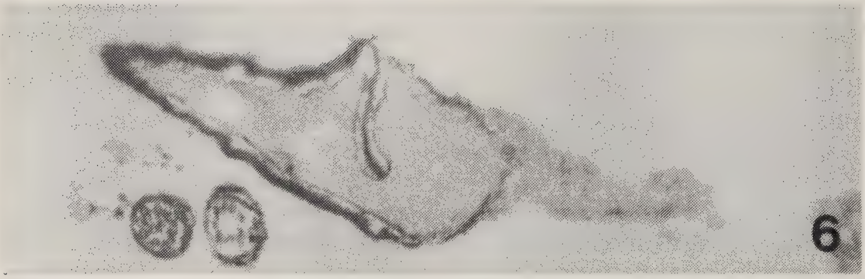
Ultrastructure of Sperm Nuclei

It is established that in men and male animals cannabis suppresses sperm production, decreases sperm motility (Hembree *et al.*, 1979; Huang *et al.*, 1979) and alters the morphology and ultrastructure of spermatozoa (Huang *et al.*, 1979; Issidorides, 1979; Zimmerman *et al.*, 1979). In the sperm samples of the chronic hashish users the structural abnormalities (in 50% of the cells) were evident in the nucleus and the acrosome (Issidorides, 1979). The findings substantiated the conclusion that chronic cannabis use mimics the sperm phenotype of a fertility problem, the so-called "idiopathic spermatidic arrest," by inducing the specific metabolic aberrations and oligospermia which characterize this pathological condition (Silvestroni *et al.*, 1976). In the process of spermatid differentiation in man the most important events are the formation of the acrosome, the nuclear condensation and the establishment of the flagellar structure. The malformations that are accompanied by infertility have been described in detail by Holstein and Schirren (1979). The authors have classified these abnormalities in human spermatids on the basis of ultrastructural studies of biopsy material from patients with fertility problems. Most classes of abnormalities described by Holstein and Schirren (1979), as indicative of infertility, are represented in samples of ejaculated spermatozoa obtained by the standard procedure from the chronic hashish users.

Examples of these classes of abnormalities are the partial invagination of the acrosome into the nucleus of the sperm (Figure 6), the separation of the acrosome from the nucleus of the spermatid (Issidorides, 1979, Figure 12) and enlarged head pieces with condensed chromatin, but lacking acrosomes (Figure 7). As a rule, acrosomes were absent from sperm heads with incomplete chromatin condensation. The various degrees of condensation in the sperm heads were clearly evident since, with the PTAH method used, totally condensed chromatin appears unstructured and homogeneously grey (Figures 8 and 9, stars) while dispersed, uncondensed chromatin appears electron-dense. The onset of chromatin condensation, which compacts the sperm nucleus into its definitive species-specific shape, is a process requiring the coordinated synthesis of specific arginine-rich histones or protamines (Coelingh *et al.*, 1969; Fawcett *et al.*, 1971), which possess unique properties for this process (Bloch and Hew, 1960; Calvin and Bedford, 1971; Godowicz, 1977). The reduction of arginine-rich proteins in the sperm of the chronic hashish users, detected by the AS reaction (Stefanis and Issidorides, 1976), has its counterpart in the patchy incomplete condensation of the chromatin, detected here by the PTAH-block-stain (Figure 8), in an otherwise normal-size sperm. A further abnormality encountered was partial ballooning of nuclei, where dispersed chromatin was organized into "hub-like" nuclear bodies (Figure 9, arrow). This state of the chromatin can be produced *in vitro* when intact human spermatozoa swell solely by their exposure to heparin (Delgado *et al.*, 1980), which is known to neutralize arginine-rich protamines (Portmann and Holden, 1949). All the described ultrastructural alterations fit the Holstein and Schirren (1979) classification of infertile sperm in human males.

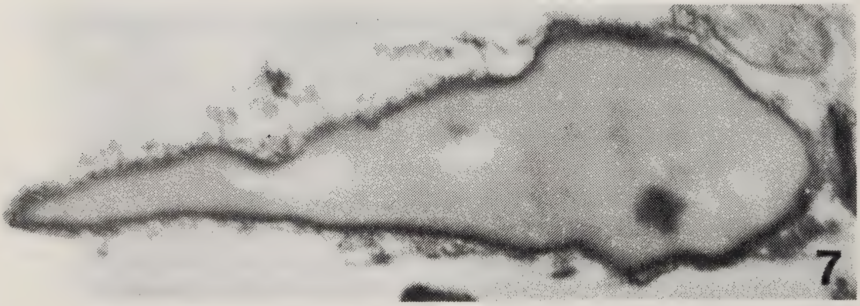
Nevertheless, impaired reproduction was not reported as a major problem by this particular group of chronic hashish users. Is there a possible explanation? Studies in fertility clinics have shown that spermatozoa within the cervical secretion, recovered 10 hr postcoitally from the female genital tract, exhibit significantly better morphology than those of the semen sample (Fredricsson and Björk, 1977), while spermatozoa in the vagina are equivalent to those in the semen sample. These findings indicated the presence of a barrier against abnormal spermatozoa at the level of the external os. The barrier was found to be particularly active against spermatozoa with abnormal heads. However, it did not appear to function in all cases encountered so that unfit spermatozoa might, under certain unexplained conditions in the female

FIGURE 6



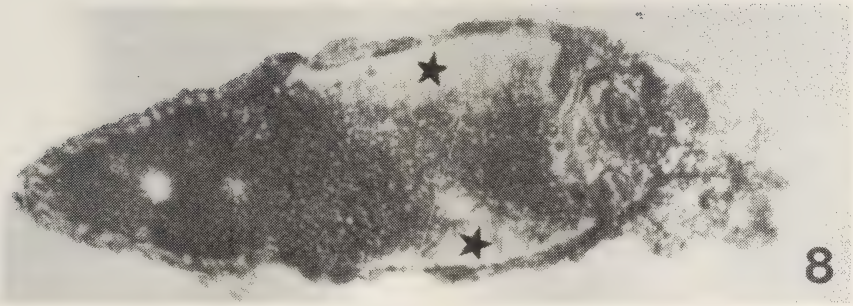
Electronmicrograph of sperm head from chronic hashish user showing condensed nucleus with invaginated acrosome. Glutaraldehyde/$KMnO_4$ fixation, PTAH-block-staining.

FIGURE 7



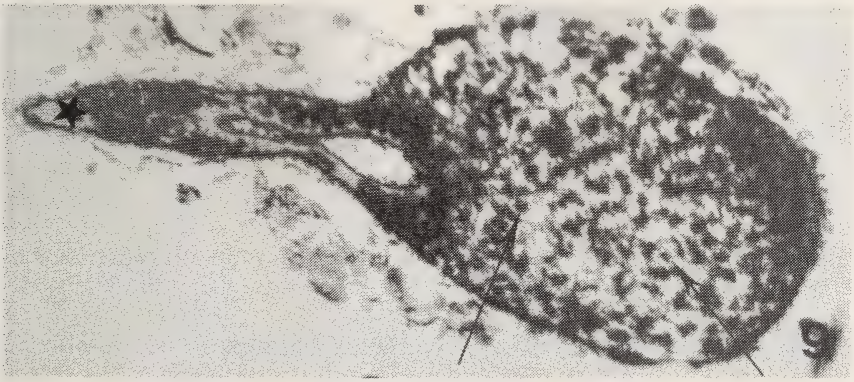
Same as Figure 6 showing enlarged head piece of condensed chromatin lacking acrosome.

FIGURE 8



Same as Figure 6 showing sperm head displaying largely partially condensed chromatin (electron-dense) and some patches of fully condensed chromatin (electron-lucent, stars). Note absence of normal acrosome.

FIGURE 9



Same as Figure 6. Sperm head swollen at the posterior end containing fully dispersed chromatin distributed in "hub-like" nuclear bodies (arrows). Note small patches of condensed chromatin (star) at anterior end; also, absence of acrosome.

genital tract, survive and reach the ovum causing effects as yet to be determined. Since the suppression in male hormone production, the decreases in the size and weight of the prostate and testes, and the inhibition of sperm production are reversible (see Bloch, this volume; Institute of Medicine, 1982) upon discontinuation of cannabis use, the question is raised regarding mechanisms that should be consistent with the overall findings. At the start it is valid to consider that cannabis produces a metabolic block in the coordinated processes of reproductive function that can presumably be reversed. Clinical observations, *in vivo* and *in vitro* trials, and data from protein chemistry support this view and add substance to the working hypothesis of a cannabis/arginine interaction.

The dependence of normal spermatogenesis on the amino acid arginine was first reported by Holt and Albanese (1944). They demonstrated first that healthy subjects on an arginine-deficient diet failed to develop negative nitrogen balances; nevertheless, a study of their seminal plasma on the ninth day of the deficiency revealed such alarmingly low figures for spermatozoa (one-tenth of normal) that the experiment was promptly terminated. The addition of an arginine supplement alone caused a prompt rise in the sperm count, but it was only after many weeks on a normal diet that entirely normal figures were restored. Holt and Albanese also found that growing rats, when placed on an arginine-deficient diet, develop demonstrable atrophic anatomical changes in the testes, as early as the third week, and that in the course of two months the disorganization of that organ becomes so complete that no evidence of spermatogenesis remains.

The histological findings of Huang and collaborators (1979) in the testes of rats with prolonged exposure to marihuana smoke are similar to those developing after arginine deprivation. Chronic treatment of rats with THC is accompanied also by a decrease in testicular weight (Harclerode *et al.*, 1979). Kolodny and collaborators (1974) were the first to report oligospermia in men who had used marihuana four days a week for at least six months. The treatment of oligospermia with the amino acid arginine was first introduced in 5 cases of idiopathic hypospermia (Holt and Albanese, 1944); definite stimulation of spermiogenesis was obtained in some patients with relapse when arginine was withdrawn. Oral or i.m. arginine administration (2 g/day for 30 days) to 15 oligospermic patients induced a significant increase in the number of spermatozoa (Garrigues, 1953). These clinical observations led to the study of human semen for the determination of free arginine and total arginine contents in samples of normal persons and of those suffering male sterility (Tanimura, 1967). The results of that study derived from determinations conducted on a total of 280 subjects. It was found that there is a positive correlation between the sperm count and the bound arginine fraction in the spermatozoa and between sperm motility and the "free" arginine content in the seminal fluid. A considerable increase in sperm count and motility was achieved with a higher dose of arginine (4 g/day) in 141 patients with various degrees of oligospermia. This observation supports the essential and multiple roles of this amino acid in fertility (Schachter *et al.*, 1973).

Proof was obtained from *in vitro* experiments in which human semen specimens with low motility were incubated with L-arginine (Keller and Polakoski, 1975). It was found that *in vitro* sperm motility followed an arginine dose-response curve which showed a positive correlation of free arginine levels with sperm motility. In that study, specificity of arginine action was suggested by the inability of d-arginine, the analogs L-homoarginine and L-nitroarginine, and L-ornithine to increase sperm motility *in vitro*. This finding indicated that the terminal guanidino in group as well as carbon chain length were essential requirements of arginine action. In recent experiments with ejaculated rabbit sperm it was found that arginine stimulated motility also in normal sperm, and that this correlated with arginine content, incubation time and pH (Radany and Atherton, 1981).

Not only *in vivo* (Hembree *et al.*, 1979) but also *in vitro* (Shahar and Bino, 1974) sperm motility is affected equally in humans and experimental animals by cannabis. The effect of cannabis and THC, however, is opposite to that of arginine. Chronic cannabis *use* decreases sperm motility (Hembree *et al.*, 1979) similarly to arginine *deprivation* (Holt and Albanese, 1944), while cannabis *abstinence* as well as arginine *supplementation*—in the respective experiments—allowed sperm motility to return to normal, but with a similarly very slow course. Reduction of bull sperm motility by THC *in vitro* was found to be dose-dependent and was accompanied by a decrease in ATP content and by swelling of the mitochondrial sheath in the midpiece of the flagellum (Shahar and Bino, 1974). The high arginine content of nuclear proteins synthesized before the end of spermatogenesis allows their intensive labeling with radioactive arginine, which in mice is maintained in mature spermatozoa up to fertilization (Monesi, 1971). Related experiments have shown that, apart from the very intense labeling of the sperm heads, there is a distinct labeling of the tails with accumulation of radioactive arginine in the midpiece (Kopeĉný and Pavlok, 1975), where the mitochondrial sheath is localized and which is considered to be the "motor" of sperm motility. It has been reported that the amino acid, acting as arginine-phosphoric acid, also serves in resynthesis of ATP, the energy-rich substance absolutely necessary for normal sperm motility (Giarola and Ballerio, 1959a and b). These last few experiments clearly indicate that THC and arginine actions overlap at the same structural site with opposite biochemical and functional effects on sperm motility.

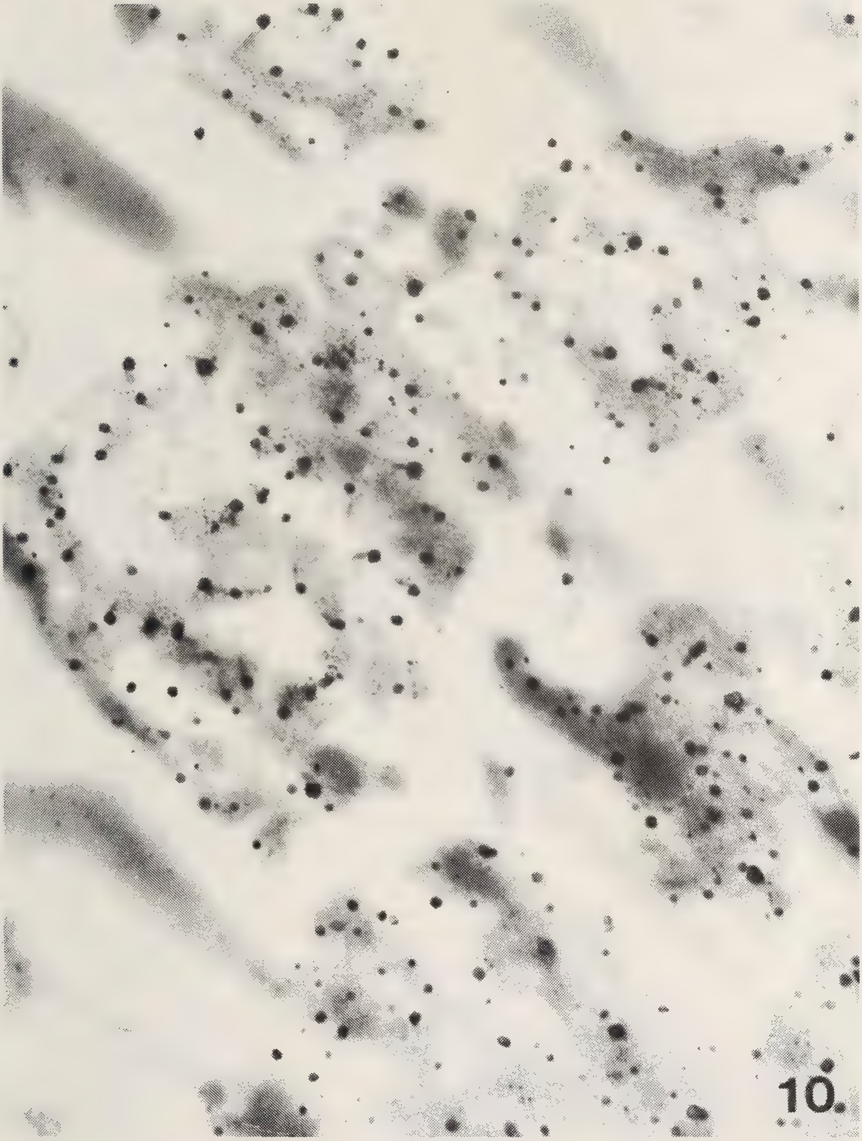
Ultrastructural Localization of Arginine-Rich Proteins in Platelets

Marihuana-induced alterations in the blood clotting mechanism have been noted by many investigators. *In vitro* exposure of human platelets to THC markedly inhibited their ADP-induced aggregation (Levy *et al.*, 1976). Similarly, the *in vivo* exposure (marihuana smoking) of human blood platelets to THC significantly decreased their aggregation *in vitro* when the response was induced by 0.5 and 1.0 μg doses of ADP (Schaefer *et al.*, 1979). It is common clinical knowledge that heparin is administered therapeutically to prevent blood clotting and that, when required, basic protamine (85% arginine) is the potent anti-heparin antidote (Portmann and Holden, 1949). Within this context, it is of interest that basic proteins with anti-heparin activity (platelet factor 4) are stored in the a-granules of human platelets (Da Prada *et al.*, 1976; Fukami *et al.*, 1979) and are released following stimulation by ADP or epinephrine (Niewiarowski *et al.*, 1968; Kaplan *et al.*, 1981). It has recently been reported that in platelets a more basic protein (PBP), with a COOH-terminal arginine, is the immunologically identical precursor of these anti-heparin clotting factors (Holt *et al.*, 1982).

In view of the effects of cannabis on the aggregation process and of its reported effects on basic proteins (Stefanis and Issidorides, 1976) the present study was initiated. It was designed to examine whether chronic cannabis use modified PBP in ways that would reflect on the platelets' decreased potential to aggregate when challenged with ADP *in vitro* (Schaefer *et al.*, 1979). Since arginine-rich proteins such as protamine (Portmann and Holden, 1949) and eosinophil major basic protein (Gleich *et al.*, 1974) share heparin-precipitating properties with the platelet anti-heparin factors, it was reasonable to use the AS reaction for arginine (MacRae and Meetz, 1970) to localize these clotting factors at the ultrastructural level. Platelets, collected from venous blood of controls and chronic hashish users, were stained *in toto* by the AS reaction after formalin-acetate fixation. They were studied without further staining of the epon thin sections, so that the only electron densities present would be those of the reaction product of silver with arginine residues of proteins.

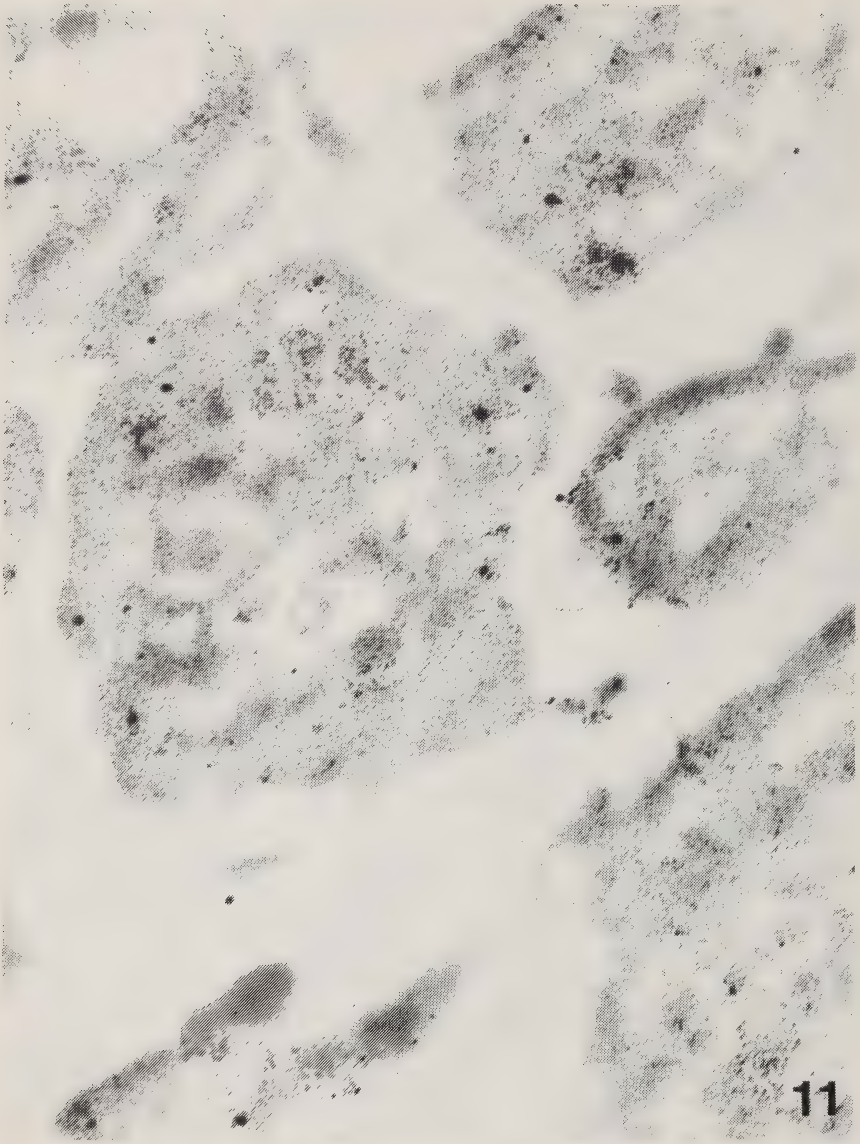
The results showed that in control subjects (Figure 10) all platelets contained numerous deposits of arginine-rich protein segregated in discrete granules of fairly uniform size. A faint diffuse reaction was noted also in the hyalomere. In chronic hashish users (Figure 11) all platelets were severely depleted of granular deposits. Measurements made on

FIGURE 10



Electronmicrograph of blood platelets from control showing numerous granular deposits and fine diffuse deposits of arginine-rich protein. The reaction pattern is uniform in all platelets. Sodium acetate — buffered formaldehyde fixation, ammoniacal silver (AS) in block-staining.

FIGURE 11



Electronmicrograph of blood platelets from chronic hashish user. Note great reduction of the granular deposits of arginine-rich protein and increase in number and size of the diffuse ones. The reaction pattern is uniform in all platelets. Sodium acetate-buffered formaldehyde fixation, ammoniacal silver (AS) in block-staining.

several platelets per section showed on the average a 90% reduction in the number of discrete granules. Although the diffuse reaction product in the hyalomere was coarser and denser than that in the controls, the overall reduction of basic proteins in the platelets of chronic users was very striking. This cytochemical localization of arginine-rich proteins in granules of human platelets is, as far as is known, reported here for the first time (Issidorides, in preparation). An earlier application of the AS reaction to glutaraldehyde-fixed rabbit platelets was designed to demonstrate the "dense" granules, for which serotonin is the marker. The demonstration was based on the affinity of silver for a serotonin-glutaraldehyde fixation product (Silver and Gardner, 1968).

Taking into consideration a) the basicity of PBP anti-heparin protein with C-terminal arginine (Holt *et al.*, 1982), b) its localization predominantly in a-granules, and c) the association of some anti-heparin activity with the amorphous fraction in sucrose density gradients of fractionated platelets (Fukami *et al.*, 1979), the suggestion is made that the AS granular and diffuse electron densities in the platelets may represent PBP macromolecules[1]. The greatly reduced quantity of such protein as observed in the platelets of chronic hashish users would be consistent with a decreased potential to aggregate in response to ADP *in vitro*. Actually, it has been known for some time that platelets contain polyamines, which derive via ornithine from arginine through the action of arginase (Cooper *et al.*, 1976). It has also been shown that polyamines inhibit *in vitro* platelet aggregation induced by ADP (Rennert *et al.*, 1976). The recent report of the isolation and 50-fold purification of a particulate arginase from human platelets (Villanueva and Giret, 1980) confirms the original observation of this activity in human platelets (Vincent *et al.*, 1962) and—in the light of our findings—integrates and justifies the proposed hypothesis of a cannabis/arginine interaction also at the level of platelet functional modulation.

Specifically, it is conceivable that, with a given concentration of substrate in platelets lacking the urea cycle and hence arginine regeneration, an increase in arginase (Table 2) activity could divert arginine into the biosynthesis of polyamines, which inhibit aggregation. This diversion could limit the arginine available for protein synthesis and incorporation into the anti-heparin PBP protein, which promotes aggregation. Interaction of cannabis with arginine in these two metabolic pathways would be sufficient to explain both the drug's inhibitory effect on ADP-induced aggregation (Schaefer *et al.*, 1979) and its depletion of arginine

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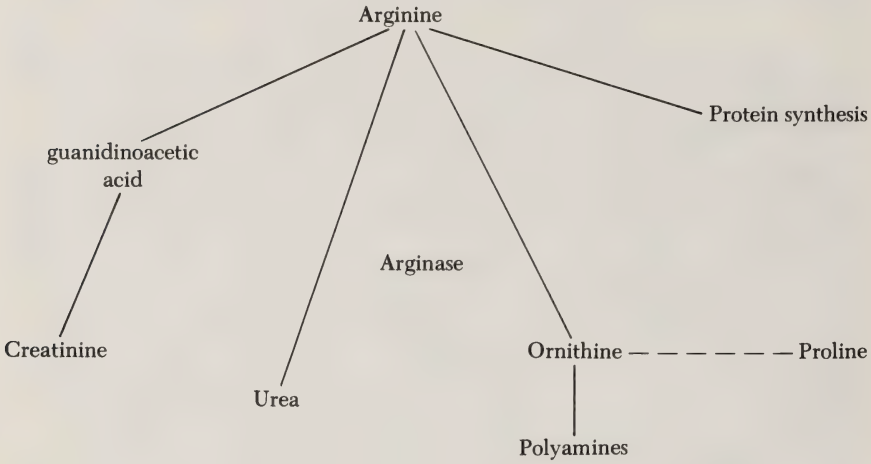
[1] The suggestion is made with caution pending results from combined immunohistochemical and fine structure studies.

TABLE 2

Pathways of Arginine Metabolism in Man


Arginine
Protein synthesis
guanidinoacetic acid
Arginase
Creatinine
Ornithine
Proline
Urea
Polyamines

proteins from their granular stores in the platelets, as demonstrated in this study.

In conclusion, platelets may now be added to the group of diverse cellular systems, including leukocytes and sperm, which uniformly suffer a reduction of their arginine-rich proteins during long-term hashish use. It clearly emerges that these cellular systems thus suffer a downgrading in the potential to subserve their particular homeostatic functions.

3. PRELIMINARY RESULTS IN BLOOD FROM PILOT STUDY ON ACUTE EFFECTS OF MARIHUANA SMOKING

Five volunteers, heavy hashish users, served as their own controls in a pilot study of the acute effects of cannabis on various structural and chemical parameters of blood. The five subjects were selected on the basis of their continuous daily smoking during the previous 30-day period. They were instructed not to use hashish for at least 12 hr before testing. The rationale of the trial was to study the blood parameters after the 12-hr abstinence period, i.e., before smoking on the day of testing, and again, at 30 min after smoking when the highest concentration of the drug in the blood is noted (Miras and Coutselinis, 1971). This time coincided with the peak of THC effects such as those on heart rate and the subjective rating of a "high." Each volunteer was allowed to smoke *ad libitum* within a period of 15 min. Home-made cigarettes contained 1 g active marihuana, supplied by NIDA (see Stefanis *et al.*, 1977), with a 2.6% THC content.

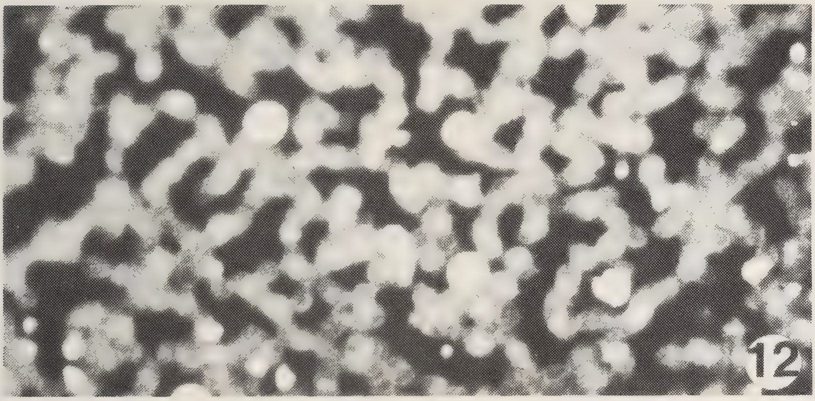
Fluorescent Product of Phenanthrenequinone with Arginine in Erythrocytes

Phenanthrenequinone (PQ) is a nonfluorescent compound reacting specifically with arginine to form a condensation product, which exhibits strong fluorescence when viewed under ultraviolet light (Yamada and Itano, 1966). The PQ reaction is an extremely sensitive and specific test for polypeptide-bound arginine in fixed tissue sections (Magun and Kelly, 1969). Because of its extreme sensitivity, the technique is recommended for the localization of arginine in specimens as thin as monolayers of cultured cells (Smith and de Harven, 1979), in smears (Magun and Kelly, 1969) and in molecules with low arginine concentration such as hemoglobin (Yamada and Itano, 1966). In view of this, the PQ reaction offered a specific tool for testing our proposed hypothesis of cannabis/arginine interaction in erythrocytes, since they represent a well known target of cannabis actions (Raz *et al.*, 1972; Chari-Bitron, 1976). Significantly elevated values for hemoglobin and packed cell volume were found in long-term ganja smokers compared to controls in the Jamaican study (Rubin and Comitas, 1975). Hence, the smokers exhibited a lowered capacity of the erythrocytes to engage oxygen. Hemoglobin within red cells reacts readily with ninhydrin (Kokkini *et al.*, 1980), which modifies the guanidino group of arginine under mild conditions (Conn and Davis, 1959; Takahashi, 1976). Increasing the amount of modification by ninhydrin was found, in the Kokkini *et al.* (1980) experiment, to decrease the oxygen affinity of the hemoglobin, thus simulating the effects of chronic ganja smoking. Since PQ generates intense fluorescence with the arginine residues of hemoglobin (Yamada and Itano, 1966), we applied this reaction to formalin fixed smears of the five subjects in the pilot study obtained before and after marihuana smoking. Brief mention will be made here of some preliminary observations (Issidorides *et al.*, unpublished results).

Available protein-bound arginine, detected by the fluorescence of its product with PQ, was observed in all smears examined. As expected, intense fluorescence developed in the leukocytes (Figure 12) where nuclear chromatin fluoresced according to its apparent condensation as observed before in other tissues (Magun and Kelly, 1969). No change in this parameter was observed in the smear of the same subject postsmoking (Figure 13). Similarly, no change was observed in fluorescence intensity of platelets, although fewer numbers were noted postsmoking. An acute effect of cannabis, however, was evident in the erythrocytes (Figure 13). The presence of the drug in the blood caused a decrease in PQ binding, hence either a reduction in available arginine or a modification of its guanidino group, which is responsible for the PQ reaction (Yamada and Itano, 1966). It should be made clear that, although this interpretation of the results is inherent in the PQ method employed, it neither restricts the observed effect of cannabis to a one-to-one chemical reaction with the amino acid, nor does it exclude it. More experiments are needed, by the pertinent disciplines, to resolve this question.

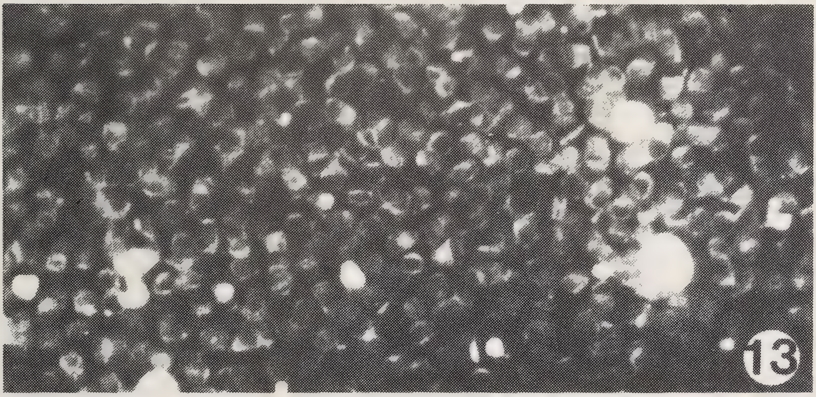
In our material, despite the limited resolution afforded by fluorescence microscopy, some additional effects were evident upon closer observation of the smears. The tendency to rouleaux formation of the "naïve" cells (Figure 12) was lost in the drug-exposed cells (Figure 13). In the latter, the arginine reaction was blocked in the interior but was more prominent in the membrane or surface, where its distribution was uneven. In the smears of drug-exposed cells, a few erythrocytes appeared enlarged, others seemed distorted; none of these parameters could, however, be assessed with confidence from the present method alone. In earlier experimental trials of a partly similar design, it was shown that erythrocytes of chronic hashish users, while comparable to those of controls before hashish smoking, displayed acute effects of the drug at 30 min after heavy use (Kalofoutis and Koutselinis, 1979; Kalofoutis *et al.*, 1980). The biochemical determinations from those trials contributed data that fit well with our cytochemical observations and provide support for the hypothesis of cannabis/arginine interactions. The first study indicated a decreased concentration of phosphatidylcholine and other membrane-bound phospholipids 30 min after heavy hashish smoking. It was suggested that this decrease through THC interaction would lead to functional alterations of membrane-bound enzyme proteins (Kalofoutis and Koutselinis, 1979). Since the results of that study were obtained from the same group of chronic hashish users from which our five volunteers were selected, it is legitimate to extrapolate

FIGURE 12



Fluorescence micrograph of blood smear from chronic hashish user prepared after 12 hr abstinence from smoking. Reaction product of phenanthrenequinone (PQ) with arginine is localized in leukocyte nuclei, in platelets and diffusely in erythrocytes. Sodium acetate-buffered formaldehyde fixation, PQ-staining.

FIGURE 13



Fluorescence micrograph of blood smear from subject in Figure 12 prepared 30 min after ad libitum *marihuana smoking. Note absence of phenanthrenequinone (PQ) /arginine fluorescence, i.e., blocking of the reaction, in a large area of each erythrocyte. Sodium acetate-buffered formaldehyde fixation, PQ-staining.*

that at the time (30 min postsmoking) when erythrocyte phospholipids were decreased, free arginine residues of the erythrocyte membrane were increased as shown by PQ fluorescence (Figure 13). Both changes resulted from the acute effect of cannabis, which, at the cytochemical level, unmasked arginyl groups.

A recent study (Akeroyd *et al.*, 1981) provided the first clear and convincing evidence that arginine residues may play an important role in phospholipid-protein interactions. Modification of the phosphatidylcholine-transfer (exchange) protein with butanedione and phenylglyoxal, which are arginine-modifying α-dicarbonyl reagents, completely inactivated the enzyme. Both reagents modified 3 out of 10 arginine residues present per protein molecule. These results revealed that arginyl residues are essential for activity, as binding sites for the negatively charged phosphate group of the phosphatidylcholine molecule. Because the various α-dicarbonyl reagents proved to be surprisingly selective for the active site residues involved in binding the anionic ligand, compared to all other arginines in the protein, it has been proposed that the microenvironment of the binding site has special properties (Patthy and Thész, 1980). Prominent among these properties was the hydrophobicity of the environment of the charges (Norne *et al.*, 1975); a proximity of positive and nonpolar groups seems to have a favorable effect upon anion binding.

There is consensus that the affinity of THC for membrane lipids may be an important factor in its molecular mode of action (Paton, 1973). Furthermore, to the question "should one think of a cannabinoid receptor?" (Mechoulam *et al.*, 1976), Paton (1976) answers that, for low doses of THC, such could be "hydrophobic spaces in membranes or *macromolecules*, the average shape and dimensions of which limit their capacity to accept larger lipophilic molecules." All data, he states, "point strongly to some special recognition site, whether it is a conventional receptor or some especially well-fitting hydrophobic site" (Paton, 1979). Our findings suggest that the hydrophobic microenvironment of essential arginines in the active sites (Norne *et al.*, 1975) of a large number of enzymes and other proteins (Riordan *et al.*, 1977; Riordan, 1979) should be seriously considered as a candidate for such a site. For example, the action of THC on red blood cell membranes causes a pronounced decrease in (Na + K)-ATPase activity (Chari-Bitron, 1976). Membrane-bound (Na + K)-ATPase was found to have essential arginyl residues at its active site (Grisham, 1979); treatment of the purified enzyme with 2,3-butanedione, a specific reagent for arginine modification, resulted in its rapid inactivation. The membrane-bound (Na + K)-ATPase must be associated with particular phospholipids for maximum activation (Farías *et al.*, 1975). Hence, THC would have the possibility to act on the lipid-protein bond and/or at the hydrophobic microenvironment of the essential arginine, presumably depending upon the dose. In support of this view, experiments on THC inactivation of other membrane-bound enzymes (Mellors, 1979) indicated that the inhibition is apparently due to a more specific interaction than that associated with the perturbation of the membrane lipid bilayer and is probably due to a specific stereochemical interaction with a hydrophobic region of the membrane or *enzyme*.

This interpretation of the observed increase in erythrocyte membrane PQ fluorescence after cannabis use has the advantage of being consistent with the biochemical data obtained from a related group of subjects under similar conditions (Kalofoutis and Koutselinis, 1979). Alternative interpretations, however, should be examined. The enzyme acetylcholinesterase (AChE), a major red cell outer surface protein (Greig *et al.*, 1953; Martin, 1970; Bender *et al.*, 1971), has 31 arginine residues (Müllner and Sund, 1980) which, if exposed, could produce PQ fluorescence. Modification of only one essential arginine out of a possible 31 with butanedione was found to cause a 70% loss of activity by distorting the conformation of the enzyme (Müllner and Sund, 1980). Since the high reactivity of essential arginines is largely due to adjacent hydrophobic sites (Norne *et al.*, 1975), since THC has affinity for hydrophobic sites, and since conformational changes of a protein may prevent or enhance reactivity of arginine with PQ (Magun and Kelly, 1969), interaction of cannabis constituents with active site arginines in AChE molecules should not be overlooked. Such an interaction would be similar to the better documented effect of cannabis treatment on ATPases discussed above, and could explain the THC-induced decrease in AChE activity in brain (Luthra *et al.*, 1975) to be discussed later.

Band 3 is the last protein which we shall consider as potentially responsible for the cannabis-induced increase in PQ/arginine fluorescence at the red cell surface. Band 3 is not only the preponderant transmembrane polypeptide of the human erythrocyte (Steck, 1974), but also has 44 arginine residues per mole protein and comprises 25% of the protein mass (Steck *et al.*, 1978). It makes up the large bulk of the total integral membrane protein of the red cell and affords a pathway for transmembrane events. Moreover, band 3 comprises the anion channel (Baines *et al.*, 1982). A close correlation has been shown between the inhibition of the facilitated diffusion of chloride and sulfate ions through the red cell membrane and the selective covalent binding of the inhibitor on band 3 at the outer surface (Cabantchik and Rothstein, 1974). The α-dicarbonyl compound 1,2-cyclohexanedione, which is known to react selectively with arginyl residues, was found to be a potent inhibitor of anion equilibrium exchange across the red blood cell (Zaki, 1981). These experiments showed that the essential arginine residues of the anion transporting site of band 3 are embedded in a hydrophobic region. It has also been shown that inhibition of chloride transport observed after ATP depletion is related to changes in membrane protein organization, which are expressed as shape changes of the erythrocyte (Motais *et al.*, 1981). Similar shape changes were observed in rat erythrocytes exposed to THC (Chari-Bitron, 1976). The unanswered question is whether the arginine-dependent chloride channel in band 3 is also a target of cannabis and whether cannabis/arginine interactions with ensuing conformational changes of the protein are responsible for the increased PQ/arginine fluorescence at the membrane (Figure 13).

It is noteworthy that all three alternative interpretations are equally dependent upon the central role of essential arginines in the function of the three membrane proteins considered. Finally, the observed blocking of intracellular erythrocyte fluorescence acutely after cannabis use was paralleled by biochemical results, i.e., a remarkable reduction in concentration of ATP and 2,3-DPG and in lactic acid production, obtained in a trial of similar design (Kalofoutis *et al.*, 1980). The authors attributed these results to the direct and rapid effect of hashish constituents on enzymes regulating the rate of glycolysis in erythrocytes. This central metabolic process is especially interesting because each step involves phosphorylated substrates or coenzymes or both; moreover, all but one of the constituent enzymes contain essential arginine residues as anion recognition sites (Riordan *et al.*, 1977). As in all previous cases discussed above, these enzymes are inactivated by butanedione modification of these arginine residues (Riordan, 1979). For example, in glyceraldehyde-3-phosphate dehydrogenase, which is associated with band 3 protein in the erythrocyte (Steck, 1974), butanedione modifies two arginine residues in each subunit, concomitant with a loss of catalytic activity (Vospelnikova *et al.*, 1981). The role of arginine not only in activity, but also in regulation, is illustrated by fructose-1,6-diphosphatase, an allosteric enzyme governing a control point of glycolysis and containing arginines both at the catalytic site and at the regulatory site that is sensitive to AMP. Modification of these arginines with butanedione was found to have bimodal effects, i.e., an initial increase and subsequent decrease in activity (Riordan *et al.*, 1977). Modification of essential arginyl residues at the regulatory (AMP) site renders the enzyme insensitive to AMP inhibition, while modification of arginyl residues at the catalytic site causes loss of enzyme activity. Cannabis/arginine interactions in the erythrocyte glycolytic pathway could explain the blocking of PQ fluorescence in the cytosol, as well as the related biochemical findings (Kalofoutis *et al.*, 1980), and could constitute a mechanism for the THC-induced paradoxical variations of specific enzymatic activities in the glycolytic pathway in other tissues (Choisy *et al.*, 1979).

Lastly, it should be mentioned that the enzyme glutathione reductase from human erythrocytes, which is involved in the protection of the red cell against conversion of hemoglobin to methemoglobin (Harper *et al.*, 1979), is inactivated by the arginine modifying reagents 2,3-butanedione, 1,2-cyclohexanedione and phenylglyoxal; the inactivation caused by these reagents increases with time and is biphasic in nature (Boggaram and Mannervik, 1982). These data illustrate how cannabis, even if acting on a "specific receptor," could cause multiple biological effects in the erythrocyte just by interfering with "essential arginine" in its fundamental role in the major metabolic pathways of this cell. The emphasis placed here on the erythrocyte was dictated by its wide use as a peripheral model possessing neuronal properties (Huestis and McConnell, 1974) and by the fact that *in vitro* affinities of several psychotropic drugs for binding sites of brain and erythrocytes are strikingly similar (Deutsch *et al.*, 1981; Tollefson *et al.*, 1982).

4. CONCLUSION

The working hypothesis of a cannabis/arginine interaction as the common denominator of the drug's multiple biological effects was formulated (Issidorides, 1979) as one reasonable interpretation of a series of experimental findings. The data discussed, both hard and soft as well as indirect (including the results from sperm, leukocytes, platelets and erythrocytes of chronic hashish users), support this interpretation.

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Immunological Effects of Cannabis

ALBERT E. MUNSON, PhD and
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1. INTRODUCTION

Cannabis is a complex plant material that can elicit a variety of pharmacological effects. After a century of clinical reports and a decade of intensive laboratory research in humans and animals, many of these are well established; the occurrence of others remains highly controversial. One of the latter areas concerns the actions of cannabis (and its psychoactive and nonpsychoactive cannabinoids) on the immune system.

The question of cannabis-induced effects on host defenses is important for two reasons. Firstly, drug-induced allergic reactions or impairment of the immune response, even if relatively mild, could become a major public health problem, given the large number of individuals in many societies who are regular users of the drug (see Mohan, this volume; Smart, this volume). Secondly, if cannabinoid-induced immunosuppression were to occur by means of a mechanism different from that of other immunosuppressants, these substances could be useful either alone or in combination with other drugs when the impairment of host defenses is clinically desirable (e.g., transplant patients).

Natural cannabinoids are unique to the plant *Cannabis sativa* L., and comprise about 15% of the 421 known constituents of the unpyrolyzed plant (Turner *et al.*, 1980). Of these, Δ^9–tetrahydrocannabinol (Δ^9–THC) is the agent believed to account for the majority, if not all, of the psychoactive effects induced by this drug. Δ^8–THC is also psychoactive, but is found in cannabis in very low concentrations. Other can-

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nabinoids including cannabinol (CBN), cannabidiol (CBD), cannabichromene (CBCh), cannabicyclol (CBC), and cannabigerol (CBG) are not psychoactive unless administered in very large doses. Both psychoactive and nonpsychoactive cannabinoids and their metabolites have been tested in a variety of *in vivo* and *in vitro* systems in order to determine the relationship between psychoactivity and possible immunosuppression. In addition, a variety of synthetic nonpsychoactive cannabinoids including 1-methyl-Δ^8-THC (1-CH_3-Δ^8-THC), abnormal Δ^8-THC (Smith *et al.*, 1978) and 8,9-epoxyhexahydrocannabinol (EHHC) (Klykken *et al.*, 1977) have been tested in the hope of developing a clinically useful immunosuppressant devoid of psychoactive effects.

Rosenkrantz (this volume) has discussed the relationship of the doses of cannabinoids commonly used in animal models to those consumed by humans. In general, behavioral effects in humans are elicited by doses of Δ^9-THC in the range of 0.08–0.16 mg/kg (5–10 mg) (Klonoff, this volume) that produce plasma Δ^9-THC levels of 40–200 ng/ml, although intake of as much as 1,000 mg/day (i.e., roughly 15 mg/kg/day) has been observed in extremely heavy users (Tennant and Groesbeck, 1972). Parenteral acute doses of greater than 10 mg/kg given to nontolerant mice and 1–10 mg/kg to rats will produce observable effects, and those in excess of 50 mg/kg in mice and rats result in marked toxicity (Rosenkrantz, this volume).

Other than some old clinical reports of poor health, emaciation, and decreased resistance to certain diseases in chronic heavy users of cannabis in Asia and Africa (see Section 5), the first suggestions of a direct effect on the immune response in man were reports that constituents of cannabis were capable of eliciting an antibody response (Liskow *et al.*, 1971) and impaired T-cell function in chronic marihuana users (Nahas *et al.*, 1973a). These reports stimulated considerable clinical and experimental research into these areas which left in its wake a body of literature full of conflicting data, and considerable debate about how the various observations should be interpreted.

In this review, we will present a brief overview of the immune system and of the mechanisms of innate and acquired defenses. We will attempt to describe and interpret the evidence that pertains to the effects of cannabinoids on each component and function of this system, to draw conclusions where possible based on the available data, and to point out areas in which further research is needed.

2. THE IMMUNE SYSTEM

The immune system of the mammalian organism is generally considered to be an adaptive and a protective mechanism against noxious foreign materials including pathogens and cancer cells. In addition, certain of the cells of the immune system are involved in maintaining homeostasis (e.g., the removal of old red blood cells or platelets by the macrophage). This system consists of organized lymphoid tissues (such as spleen and lymph nodes), the central lymphoid elements (thymus and bone marrow), and the recirculating pool of lymphocytes (Paul, 1980). The cells constituting the immune system are derived from bone marrow stem cells (Figure 1). Their roles, described below and in Section 4, can be readily separated into those that are innate and those that are acquired.

Innate Immunity

Innate immunity consists of those responses to foreign substances that do not require previous sensitization and is critical to the survival of the host. Examples of these responses are the phagocytosis of bacteria by polymorphonuclear (PMN) leukocytes and macrophages. The diseases involving either a decreased number of PMN leukocytes or a defect in their ability to phagocytize testify to the importance of these functions.

Also involved in innate immunity is the natural killer (NK) cell which is capable of killing a tumor cell without having been exposed to it previously. Another example of innate immunity not related to stem-cell-derived cells is the cough reflex, which, when suppressed, can lead to an exacerbation of pneumonia and death.

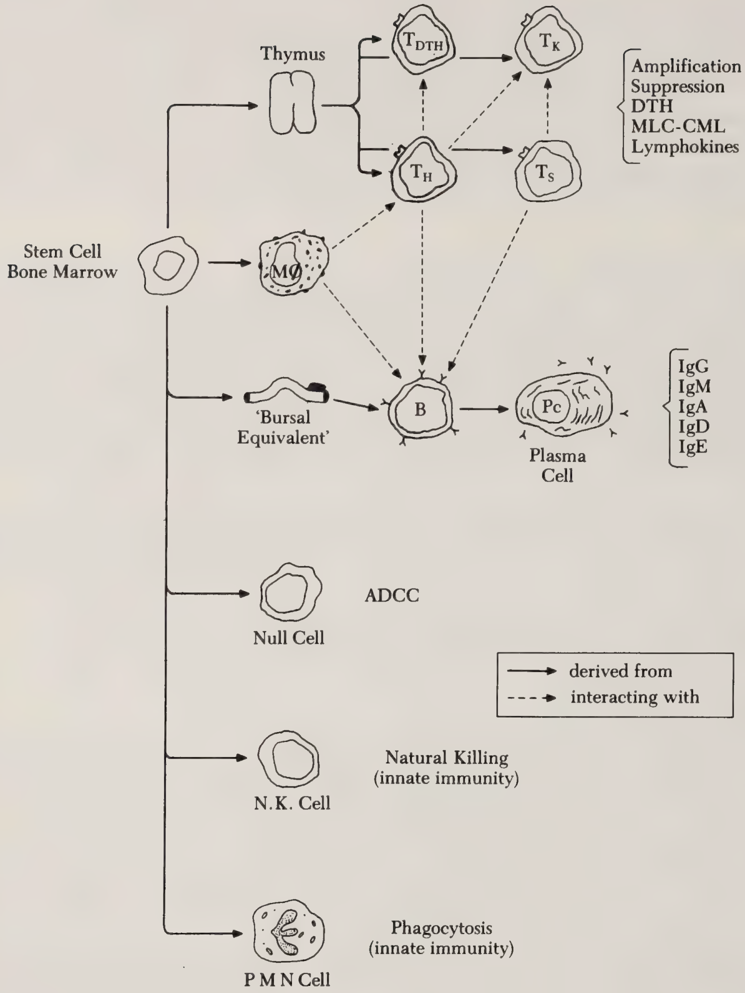
Acquired Immunity

Often, however, the destruction of a foreign material is dependent on processes generated by previous exposure to that substance. This so-called acquired immunity is largely mediated by the cooperative function of three major families of cells derived from stem cells: thymus-dependent lymphocytes (T-cells), thymus-independent lymphocytes (B-cells), and monocyte/macrophages. There is also a contribution by some specialized epithelial cells and by structural elements in organized lymphoid tissues such as thymus, spleen, and lymph nodes. The functions of the two major arms of the immune system, humoral immunity and cell-mediated immunity, are summarized briefly below and are described in more detail in Section 4.

Humoral Immunity

Humoral immunity, i.e., the production of antibodies in response to foreign material (antigen), is related to the bursa-dependent lymphocytes (B-cells). These cells are derived from a stem cell, and in the bird, undergo differentiation in a central lymphoepithelial organ, the

FIGURE 1


Thymus
T_{DTH}
T_K
T_H
T_S
Amplification
Suppression
DTH
MLC-CML
Lymphokines
Stem Cell
Bone Marrow
MØ
'Bursal
Equivalent'
B
Pc
Plasma
Cell
IgG
IgM
IgA
IgD
IgE
Null Cell
ADCC
derived from
interacting with
N.K. Cell
Natural Killing
(innate immunity)
P M N Cell
Phagocytosis
(innate immunity)

Schematic diagram of the immune system. Lymphocytes include T-delayed type hypersensitivity (T_{DTH}) cells, T-killer (T_K) cells, T-helper (T_H) cells and T-suppressor (T_S) cells, B-cells (B), null cells, and natural killer (NK) cells. Other cells include macrophages (MΦ) and polymorphonuclear (PMN) leukocytes. MLC-CML denotes mixed lymphocyte culture cell-mediated lysis; ADCC, antibody dependent cell-mediated cytotoxicity. (Courtesy P.H. Bick, Dept. of Microbiology, Medical College of Virginia).

bursa of Fabricius. The bursal equivalent area in mammals is not known but is at present suspected to be in the bone marrow itself.

The response of the mature B-lymphocyte is triggered by a foreign substance, usually a protein, called an antigen which can be free, or attached to the surface of a foreign cell. Immunoglobulins (Ig) on the surface of the B-cells serve as receptors to initiate the reaction. The generally accepted theory of clonal selection states that the antigen stimulates a small population of lymphoid cells that possess a receptor for it. These cells proliferate, mature, and differentiate, thus producing large populations of antigen-specific cells (Rowley *et al.*, 1973). Some antigens, especially those with repeating subunits such as *Escherichia coli* lipopolysaccharide (LPS), can stimulate B-cells directly (Andersson and Blomgren, 1971). Most others require the assistance of the macrophages and T-helper (T_H) cells to present the antigen to the B-cell. Another subpopulation of T-cells, the T-suppressor (T_S) cells, can suppress this response.

The differentiation of stimulated B-cells produces plasma cells that synthesize and release antibody, and memory B-cells which remain as resting antigen-sensitized cells and can respond on subsequent exposure by the rapid release of large amounts of antibody (Andrews and Capra, 1980). The type of immunoglobulin produced is a function of the type of antigen and the time after exposure. Generally IgM is the earliest immunoglobulin produced, followed by IgG. IgA is a secretory antibody generally associated with the mucosae of the gastrointestinal and respiratory tracts. IgE is the antibody associated with immediate hypersensitivity reactions such as those seen in anaphylactic shock and asthma. The exact nature of the IgD immunoglobulin is not known. However, the general consensus is that it regulates certain aspects of the immune system.

The purpose of the antibodies is to recognize foreign molecules or organisms possessing specific antigens and to assist in the elimination of these substances from the body. Their production is very important in the defense against most bacterial infections, certain viral infections, and a few fungal infections. The binding of the antibody to the foreign antigen can directly inactivate pathogens or toxins by the actual physical masking of their receptor sites or it can allow at least two other possible reactions to take place. One is that the antibody, in the presence of antigen, will fix complement. This initiates the complement cascade which results in the eventual lysis or damage to the membrane of the antigen-containing cell. The second is the antibody-dependent cell-mediated cytotoxicity reaction (ADCC). In this case the immunoglobulin bound to the antigen is recognized by two different types of cells: the null cell and the macrophage. The macrophage can either phagocytize the cell covered with antibody-coated antigen and kill it intracellularly, or can kill it through the release of certain toxic substances. The null cell does not have the ability to phagocytize but does recognize the antibody-coated cell and can also kill it by releasing toxins.

Cell-Mediated Immunity

Cell-mediated immunity, which is directed against foreign cells and against many bacteria, viruses, and fungi, is dependent on the function of T-lymphocytes. These cells are also derived from a stem cell, differentiate and mature in the thymus gland, and consist of at least four discrete subpopulations: T-delayed type hypersensitivity (T_{DTH}), T-killer (T_K), T_H, and T_S cells (Figure 1). The initial presentation of antigen (often by the macrophages) stimulates the proliferation of clones of cells with specific receptors for that antigen (cf., the description of B-cell activation in Section 4). These cells remain in the circulation in an activated state and when re-exposed to the same antigen, they undergo blast transformation. T_K-cells are then capable of killing antigen-bearing cells (cell-mediated cytotoxicity). T_{DTH}-cells produce substances known as lymphokines that attract, immobilize, or otherwise modify the functions of other cells such as macrophages, neutrophils, eosinophils, and basophils (Waksman, 1980). The most extensively studied lymphokine, macrophage inhibition factor (MIF), acts on passing monocytes to make them adhere to capillary walls in the vicinity of the reaction, and perhaps, to activate them. Other lymphokines can lyse certain cell types (lymphotoxin), increase resistance to viruses (interferon), or inhibit DNA synthesis. These processes result in skin reactions with a delayed time course such as the delayed cutaneous hypersensitivity response (e.g., contact allergies) and in tissue-destructive lesions such as allograft rejection. A deficiency in these responses leads to inadequate host defense.

The macrophage, also derived from a bone marrow stem cell, is the other cell involved in cell-mediated immunity. Present in the blood for up to three days as the monocyte, it becomes a macrophage as it moves into the tissues. These cells are intimately involved in the early removal of foreign materials and, in most cases, are important in phagocytizing and altering antigens and presenting them to the T- or B-lymphocytes for the further development of the immune response. Macrophages are also important in the final effector mechanisms of the response, i.e., the DTH and the ADCC, and thus are involved in the final removal of antigens from the organism. Related cells are also found in connective tissue (histiocytes), liver (Kupffer cells), lung (alveolar macrophages), and nervous tissue (microglia). Major defects in macrophage function or number are incompatible with a normal immune response.

Another cell believed to be involved in cell-mediated immunity is the null cell. This stem-cell-derived lymphoctye can be differentiated from T-cells and B-cells by the absence of surface receptors, and is involved in the ADCC by destroying antibody-coated nucleated cells. This process is not dependent on the presence of complement.

The individual cells of the immune system, i.e., the T-cells, B-cells, the macrophages, the NK and the null cells work in concert to protect the organism from all pathogens. There is overlap in their function which does allow certain safety factors. However, perturbations in these functions can provide the pathogen with the opportunity to gain an advantage in the host-parasite interaction. The evidence with respect to the occurrence of a cannabinoid-induced immunosuppression and its possible significance will be discussed in the following sections.

3. EFFECTS ON LYMPHOID ORGANS

Nonspecific immunosuppression is often suggested by a reduction in weight of lymphoid organs, by a decrease in the numbers of lymphocytes demonstrable in these tissues, or by a change in the leukocyte differential appearing as a decrease in the lymphocyte/granulocyte ratio or a loss of monocytes. For this reason, several investigators have performed gross anatomical and histological studies on the effects of cannabis derivatives on lymphoid tissues and cells. The results of 37 such studies are summarized in Table 1.

Effects on Stem Cells

Since all immunocompetent cells are derived from stem cells, the effects of the drug on bone marrow have been examined by a number of investigators. Chronic or subchronic treatment with very large doses of Δ^9–THC (up to 500 mg/kg p.o.) has resulted in myeloid hyperplasia of the bone marrow of Rhesus monkeys (Thompson *et al.*, 1974) and fatty infiltration and hypocellularity of the sternal bone marrow in rats (Thompson *et al.*, 1973). No change in cellularity was observed by these investigators in rat femoral bone marrow. Joneja and Kaiserman (1978) using acute s.c. doses as low as 10 mg/kg in hamsters demonstrated a reduced mitotic index in bone marrow cells, while Carchman *et al.* (1976) found that concentrations in the order of 10–100 μM Δ^9–THC inhibited *in vitro* DNA synthesis in cultures of bone marrow cells as reflected by a decreased incorporation of radiolabeled thymidine. These studies demonstrate a toxic effect of Δ^9–THC on bone marrow cells in

TABLE 1

Changes in Lymphoid Parameters

Species	Sex/Strain	Cannabinoid/ Dose (mg/kg)/ Route	Duration of Exposure	Lymph Nodes
Man	♂	Δ^9–THC in C[a] Smoke/h[b]/ inhalation	several months	
Man	♂	Δ^9–THC in C Smoke/m[c],h/ inhalation	5.2 yr	
Man	♂	Δ^9–THC in C Smoke/m,h/ inhalation	⩾1 yr	
Man	♂	Δ^9–THC in C Smoke/h/ inhalation	>7 yr	
Man	♂	Δ^9–THC in C Smoke/h/ inhalation	>10 yr	
Man	♂	Δ^9–THC, Δ^9–THC in CCE[d]/210/p.o.	up to 21 days	
Man	♂	Δ^9–THC in C Smoke/0.3/ inhalation	64 days	
Man	♂	Δ^9–THC in C Smoke/h/ inhalation	>10 yr	

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a) cannabis b) heavy user (⩾ once/day) c) moderate user (1–6/week)
d) crude cannabis extract e) absolute weight f) relative weight g) no change
h) increase i) decrease

ervations		Leukocytes		
Spleen	Thymus	Total	Lymphocytes	Reference
		→[g]	% →	Tennant *et al.*, 1971
		→	% →	Bernstein *et al.*, 1974
			% →	Petersen *et al.*, 1976
		→	% →	Rubin and Comitas, 1975
		→	% →	Coggins *et al.*, 1976
		no change reported	no change reported	Jones *et al.*, 1976
		→	% →	Rachelefsky *et al.*, 1976
			arginine rich histones ↓[i]	Stefanis and Issidorides, 1976
			ultrastructural changes	Issidorides, 1979

TABLE 1 (CONTINUED)

Species	Sex/Strain	Cannabinoid/ Dose (mg/kg)/ Route	Duration of Exposure	Lymph Nodes
Man	♂	Δ⁹–THC in C Smoke/1–3/ inhalation	28 days	
Man	♂	Δ⁹–THC in C Smoke, leaf/h/ inhalation/ p.o.	>5 yr	
Monkey	♂, ♀/Rhesus	Δ⁹–THC in CCE/13–300/ p.o.	51 days	
Monkey	♂, ♀/Rhesus	Δ⁹–THC/ 5–45/i.v. 50–500/p.o.	28 days	
Monkey	?/Cynomolgus	Δ⁹–THC in C Smoke/6–14/ inhalation	360 days	
Dog	?/?	Δ⁹–THC in C resin/ 3,000 (resin)/ p.o.	up to 70 days	
Dog	♀/Beagle	Δ⁹–THC in C Smoke/ 5.5/inhalation	270 days	
Dog	♀/Beagle	Δ⁹–THC in C Smoke/ 4.8/inhalation	2.5 yr	
Dog	♀/Beagle	Δ⁹–THC in C Smoke/1.4/ inhalation	360 days	deposition of pigment

servations		Leukocytes		
Spleen	Thymus	Total	Lymphocytes	Reference
			total →	Cushman and Khurana, 1977
		no change reported	no change reported	Wig and Varma, 1977
		no change reported	no change reported	Stadnicki *et al.*, 1974
wt (A)[e] →	wt (A) ↓	↑[h]	no change reported	Thompson *et al.*, 1974
wt (A) →	wt (A) →	no change reported	no change reported	Coate and Voelker, 1979
histopathology		↑	% ↑	Durandina and Romasenko, 1972
			% ↓	Huy *et al.*, 1975a
wt (R)[f] →				Huy and Roy, 1976
no histopathology		→	% →	Sullivan and Willard, 1978

TABLE 1 (CONTINUED)

Species	Sex/Strain	Cannabinoid/ Dose (mg/kg)/ Route	Duration of Exposure	Lymph Nodes
Rabbit	♀/New Zealand albino	Δ^9–THC/ 50–150/s.c.	28 days	
Rabbit	♀ /New Zealand albino	Δ^9–THC/ 3–100/s.c.	13 days	
Guinea pig	♂ /English shorthair	Δ^9–THC/ 3/i.p.	180 days	
Guinea pig	♂ /?	C dust/ ?/inhalation	180 days	large pyroninophilic cells lymphocytes ↑[h]
Rat	♂ /Sprague-Dawley	Δ^9–THC in C Smoke/ 0.1–0.5/ inhalation	42 days	
Rat	♂ /Holtzman	Δ^9–THC/ 4–30/i.p.	30 days	
Rat	♂, ♀ /Fischer	Δ^9–THC, Δ^8–THC, Δ^9–THC in CCE/50–500/ p.o.	119 days	
Rat	♂, ♀ /Fischer	Δ^9–THC in C Smoke/0.7–4/ inhalation	23 days	
Rat	♂, ♀ /Fischer	Δ^9–THC in C Smoke/0.7–4/ inhalation	87 days	

ervations		Leukocytes		
Spleen	Thymus	Total	Lymphocytes	Reference
		→	% →	Thompson *et al.*, 1975
wt (R) → no histopathology		→	% →	Banerjee *et al.*, 1976
wt (R) ↓				Huy *et al.*, 1975b
				Shanker *et al.*, 1978
wt (A) →				Ho *et al.*, 1971
no change in wt reported				Phillips *et al.*, 1972
wt (R) ↓ hypocellularity		↓ (mild)	no change reported	Thompson *et al.*, 1973
sex-related inconsistent changes in wt	focal hemorrhages	→	→	Rosenkrantz and Braude, 1974
no change in wt reported		no change reported	no change reported	Fleischman *et al.*, 1975

TABLE 1 (CONTINUED)

Species	Sex/Strain	Cannabinoid/ Dose/Route (mg/kg)	Duration of Exposure	Lymph Nodes
Rat	♂ , ♀ /Fischer	Δ^9–THC/ 2–50/p.o.	180 days	
Rat	♀ /Fischer	Δ^9–THC/ 1–10/p.o.	3–5 days	
Rat	♂ , ♀ /Fischer	Δ^9–THC/ 1–10/p.o.	5 days	
		Δ^9–THC in C Smoke/0.7–4.0/ inhalation	5 days	
Rat	♂ ,♀ /Fischer	Δ^9–THC/ 6–12/p.o.	5–26 days	
Mouse	?/Swiss Webster	Δ^9–THC/ 100/i.p.	5 days	
Mouse	♂ /BDF$_1$	Δ^9–THC/ 10–40/i.p.	7–8 days	
Mouse	♂ /BDF$_1$	Δ^9–THC/ 25/i.p.	5 days	
Mouse	♂ /NYLAR–A	Δ^9–THC/ 25–200/p.o.	1 day	
Mouse	?/?	Δ^9–THC up to 200/p.o.	6 days	
Mouse	♂ /BDF$_1$ CDF$_1$	EHHC/25–100/ i.p.	1 day	

ervations		Leukocytes		
Spleen	Thymus	Total	Lymphocytes	Reference
wt (R) →	wt (R) →	no consistent changes	→	Rosenkrantz *et al.*, 1975b
wt (R) →				Rosenkrantz *et al.*, 1975a
wt (R) ↓				Rosenkrantz, 1976
wt (R) ↓				
dose- and sex-related wt changes	dose- and sex-related wt changes			Luthra *et al.*, 1980
wt (A) ↓	wt (A) ↓			Lefkowitz and Chiang, 1975
wt (A) ↓ hypocellularity				Lefkowitz *et al.*, 1978
wt (A) ↓ hypocellularity				Pruess and Lefkowitz, 1978
transient wt (A) ↓		transient ↓		Munson *et al.*, 1976
transient hypocellularity				
wt (A) ↓				Petersen and Lemberger, 1976
wt (A) ↓ hypocellularity		↓		Klykken *et al.*, 1977

TABLE 1 (CONTINUED)

Species	Sex/Strain	Cannabinoid/ Dose/Route (mg/kg)	Duration of Exposure	Lymph Nodes
Mouse	♂/CD-1	Δ^9-THC/1-10/ i.p.	4 days	
		CBD,CBN/ 25/i.p.		
Mouse	♀/CDF$_1$	1-CH_3-Δ^8 -THC/200/s.c.	4 days	cellularity →

general, but do not indicate a specific effect on stem cells. Johnson and Wiersema (1974a and b) administered an i.v. dose of 50 mg/kg Δ^9-THC to rats subacutely. The drug appeared to prevent myelopoiesis and to accelerate lymphocyte maturation in bone marrow. Since pretreatment with the metabolic inhibitor SKF-525A abolished the Δ^9-THC-induced response, the authors concluded that a metabolite, probably 11-OH-Δ^9-THC, was mainly responsible for the observed effect. High doses of cannabinoids can, therefore, affect stem cell function. Whether this action produces secondary effects on the competence of the immune system is still unkown.

Effects on Leukocytes

An examination of Table 1 reveals that there are no consistent changes in the total number of leukocytes or the leukocyte differential after acute or chronic administration of cannabinoids in humans. Mild transient decreases in total leukocytes were reported in rats (Thompson *et al.*, 1973) and mice (Munson *et al.*, 1976; Klykken *et al.*, 1977) at doses of cannabinoids greater than 100 mg/kg, while increases were reported in dogs (Durandina and Romasenko, 1972) and monkeys (Thompson *et al.*, 1974) also treated with high doses. Most investigators observed no changes. Similarly, no change in the percentage of lymphocytes was reported by most authors, although both an increase

vations		Leukocytes		
Spleen	Thymus	Total	Lymphocytes	Reference
wt (R) ↓ $\frac{\text{white pulp}}{\text{total volume}} \downarrow$				Zimmerman *et al.*, 1977
cellularity →	cellularity ↓			Smith, 1979

(Durandina and Romasenko, 1972) and a decrease (Huy and Roy, 1976) have been noted in dogs after chronic treatment. Overall then, there appears to be very little change in leukocyte parameters at doses relevant to those used by humans (Rosenkrantz, this volume). Transient changes reported in mice may be due in part to cannabinoid-induced release of corticosteroids (Smith, 1979).

One group (Stefanis and Issidorides, 1976) has observed a decrease in arginine-rich histones in the nuclei of lymphocytes harvested from chronic heavy cannabis users in Greece. This was accompanied by abnormal condensation of chromatin and changes in the nuclear boundaries that suggested the arrest of transcription (Issidorides, 1979). These changes, although still unconfirmed, are interesting and could possibly reflect a disruption in the synthesis of macromolecules (see Section 7).

Effects on the Thymus

As noted in Section 2, the differentiation of T-lymphocytes occurs in the thymus. This gland is fully developed at birth, and gradually atrophies with age. There are reports (Table 1) of decreases in absolute thymic weights in Rhesus monkeys (Thompson *et al.*, 1974) and mice (Lefkowitz and Chiang, 1975) after relatively short periods of treatment. Similarly, Luthra *et al.* (1980) observed changes in rats that were dose-

and sex-related. No change in absolute weight was reported in Cynomolgus monkeys (Coate and Voelker, 1979) and rats (Rosenkrantz *et al.*, 1975b) treated for periods of at least six months. It is possible that investigators using longer treatment periods observed the development of tolerance to cannabis-induced changes in thymic weight. The doses, routes of administration, and cannabis preparations were so different in these studies, however, that definite conclusions are difficult to draw. There are no reports of histopathological changes in animals showing thymic weight decreases, so it is unknown whether cortical or medullary lymphocytes were being lost.

Effects on Lymph Nodes

The lymph nodes are organs with a variety of different functions. On entering the lymph node from the circulation, B-cells tend to migrate toward the cortex where they can be converted to plasma cells and secrete antibodies. T-cells move mainly to paracortical areas where they can proliferate if stimulated. Both types of lymphocytes are continually leaving the lymph nodes through efferent ducts and re-entering the circulation via the thoracic duct. The lymph nodes of cannabis-treated animals have rarely been examined (Table 1). Smith (1979) reported no change in lymph node cellularity in mice treated subacutely with 1-CH_3-Δ^8-THC. Sullivan and Willard (1978) observed the deposition of pigment in the lymph nodes of dogs exposed to cannabis smoke for one year and Shanker *et al.* (1978) described large pyroninophilic cells and an increase in lymphocytes in the lymph nodes of guinea pigs chronically treated with cannabis dust. The significance of these latter observations is not clear.

Effects on Spleen

The spleen is a specific filter through which circulating blood and lymphatic fluid pass. It contains both red pulp which is rich in erythrocytes and white pulp which is mainly composed of lymphocytes. It also stores platelets and granulocytes. As can be seen from Table 1, the effects of cannabinoids on the relative and absolute spleen weights of experimental animals have been variable. In monkeys, dogs, and rabbits there have been no consistent changes in splenic weight although there is one report of histopathology in dogs (Durandina and Romasenko, 1972) after treatment with what appeared to be very high doses. In guinea pigs and rats, changes have been nonexistent or inconsistent, depending to some extent on the sex of the animal (Rosenkrantz and Braude, 1974; Luthra *et al.*, 1980). In Δ^9-THC- or EHHC-treated mice there has been a consistent decrease in absolute weights and a transient hypocellularity (see Table 1). There is also one report of a decrease in the ratio of white pulp volume to total spleen volume (Zimmerman *et al.*, 1977). Treatment with 1-CH_3-Δ^8-THC, however, did not produce hypocellularity

(Smith, 1979). The rodent experiments in which the shortest treatment durations were used (which included all of the mouse experiments) tended to demonstrate the most marked effects. This may reflect either the development of tolerance to cannabinoid-induced effects in the longer experiments, or the fact that higher doses were generally used in the shorter studies.

Weight loss in the rodent spleen is better correlated with immunosupression than the same effect in higher mammals. The rodent spleen does not have a strong capsule and tends to lose lymphocytes easily. In higher animals with stronger splenic capsules, spleen weight is much more dependent on the amount of blood present, and is often highly variable. Therefore it is not surprising to find the best evidence of cannabis-induced changes in rodent spleens.

Corticosteroid release is known to affect splenic cellularity (Claman, 1972). In man, this is probably brought about by a redistribution of splenic lymphocytes to the bone marrow, whereas in the mouse, corticosteroids appear to be lympholytic. Smith (1979) demonstrated that Δ^9-THC-induced reduction in splenic weight and loss of cellularity observed in normal animals do not occur in adrenalectomized mice. This suggests that cannabinoids may produce this effect indirectly by causing the release of steroids via stimulation of the pituitary-adrenal axis (see Section 7).

4. EFFECTS ON ACQUIRED IMMUNITY

Drug-induced effects on acquired immunity can be examined in all the cell types described in Section 2, including T- and B-lymphocytes and macrophages. In this section the effects of cannabinoids on both cell-mediated and humoral immunity will be reviewed.

Effects on Humoral Immunity

As explained in Section 2, humoral immunity is expressed by the formation of antibodies by activated B-cells. The function of these cells is difficult to evaluate directly, since many of the antigen-initiated processes are under the control of certain T-cells. Assessments of the competence of this system generally include enumeration of B-cells and studies of their function. The latter can involve determinations of the proliferative response to antigens or increases in immunoglobulin synthesis after stimulation. The relevant techniques will be described below.

Enumeration of B-cells

B-lymphocytes can be identified by their surface receptors for complement and by their membrane-associated immunoglobulins (Paul, 1980). The two assays used in the cannabis literature involve either treating the lymphocytes with an anti-immunoglobulin conjugated with a fluorescent stain (IgB-cells) or measuring the number of lymphocytes (EAC complexes) which bind sheep erythrocytes (sRBC) that have been coated with antibody and complement. The formation of EAC rosettes depends on the presence of a receptor for the activated third component of complement (C3) that occurs on the surface of B-cells.

In man, cannabis does not consistently alter the number or percentage of B-cells as determined by the immunofluorescent or EAC rosette techniques (Table 2) although Gupta *et al.* (1974) reported more variation among their marihuana-using subjects than is commonly observed among nonsmokers. Decreases in the number of B-cells forming rosettes have been reported in mice treated for up to eight days with doses of Δ^9-THC ranging from 10–40 mg/kg (Lefkowitz *et al.*, 1978). Immature mice (four weeks old) were more sensitive to the effects of the drug than mature mice (Pruess and Lefkowitz, 1978).

Function of B-cells

B-cell function can be evaluated by measuring the *in vitro* proliferative response to polyclonal activators (B-cell mitogens) or by assessing either the basal production of antibodies or their synthesis in response to stimulation by specific antigens.

Response to Mitogens: A number of substances can induce B-cells to proliferate and secrete antibodies by binding to nonimmunoglobulin receptors on the cell membranes. This interaction is therefore not dependent on antigen specificity, and a large population of B-cells can be stimulated. These substances are known as polyclonal B-cell activators or mitogens (Paul, 1980). The B-cell response to the mitogen (i.e., the formation of lymphoblasts or blastogenesis) is assessed by the degree of incorporation of radiolabeled thymidine into DNA, although this quantitative method may have limitations (Munson, 1975). A number of substances including bacterial LPS and pokeweed mitogen are effective B-cell mitogens in the mouse. In man, only pokeweed mitogen is a useful stimulator of B-cells, and this substance produces some activation of T-cells as well.

White *et al.* (1975) found no difference in the *in vitro* responsiveness to pokeweed mitogen between lymphocyte cultures from human marihuana smokers and nonsmokers (Table 2). Daul and Heath (1975) did note a reversible decrease in responsiveness to pokeweed mitogen in four of five Rhesus monkeys treated for six months with cannabis smoke. The differences were not dose-related, and not significant. Munson *et al.* (1976) reported a significant decrease in the *in vitro* response to bacterial

LPS in lymphocytes obtained from mice treated with doses of Δ^9–THC equal to or greater than 50 mg/kg. Treatment for 16 consecutive days with 25 mg/kg also significantly reduced responsiveness. Unfortunately, lower doses were not used in the subchronic study, so the threshold dose is not known.

In the mouse, therefore, it appears that Δ^9–THC can impair the response of the B-cell to mitogens, and the sensitivity increases with subchronic treatment. In man, a similar effect has not been demonstrated.

Antibody Formation: It is useful to determine basal serum antibody levels in humans or animals, since abnormally low levels may be suggestive of immunosuppression. For example, abnormally low levels of circulating IgG have been observed in mice treated for 14 consecutive days with 30 mg/kg cyclophosphamide (Munson *et al.*, 1982). Immunoglobulins are most easily quantitated by the use of heterologous antisera (e.g., by immunodiffusion).

Cannabinoid-induced effects on basal antibody levels are summarized in Table 2. In man, there are no consistent changes evident. One group (Rachelefsky *et al.*, 1976) noted an increase in IgE in 30% of their subjects who smoked cannabis in an experimental research ward for 64 days, possibly because components of cannabis can function as allergens (see below). Another group (Shapiro *et al.*, 1976) observed decreased IgA levels in 25% of their subjects, and decreased IgG levels in 6%. Interpretation of these findings is made difficult by the fact that some of the subjects had had as few as 20 exposures to marihuana, and nearly a third had not smoked for at least six months. In addition, routine laboratory tests revealed liver dysfunction in 30% of the users, although it is not stated whether these subjects were the same as those with reduced immunoglobulin levels. Nahas *et al.* (1979) reported that IgG levels were significantly lower in a group of cannabis users than in a group of nonusing controls. The users' mean IgG level (985 mg/dl), however, was within normal limits (Stiehm and Fudenberg, 1966) and rose during the course of four weeks of experimental administration of marihuana.

There is one report (Daul and Heath, 1975) of reduced plasma levels of IgG and IgM in Rhesus monkeys treated for six months with cannabis smoke. The small number of monkeys affected (three) and the use of human antisera make the significance of this report difficult to evaluate. Basal immunoglobulin levels have not been studied in cannabis-treated rodents, since until recently antisera have not been available.

Because of the relatively long half-life of immunoglobulins, a

TABLE 2

Suppression of Humoral Immunity

Species	Sex/Strain	Drug	*In Vitro* Concentration (μM)	*In Vivo* Dose (mg/kg/day)/ Route/Duration of Exposure	Immunoglobulin Levels
Man	♂, ♀	Δ^9–THC in C[a] Smoke		≥m[b]/inhalation/ >1 yr	
Man	♂	Δ^9–THC in C Smoke		m,h[c]/inhalation	IgG →[e] IgM → IgA → Complement →
Man	♂, ♀	Δ^9–THC in C Smoke		≥m/inhalation/ >1 yr	
Man	♂	Δ^9–THC in C Smoke		≥0.3/inhalation/ 64 days	IgG → IgM → IgA → IgE ↑ (30% Ss)
Man	?	Δ^9–THC in C Smoke		?/inhalation >20 times	IgA ↓[g] (25% Ss) IgG ↓ (6% Ss) IgM → Complement →

a) cannabis b) moderate user (1–6/week) c) heavy user (≥ once/day)
d) antibody-forming cells e) no change f) increase g) decrease
h) plaque-forming cells

Observations				
PFC[d]	Serum Antibody Titers	Mitogenicity	Enumeration of B-Cells	Reference
			EAC rosettes →	Gupta *et al.*, 1974
			% IgB cells trend ↑[f]	Petersen *et al.*, 1975
		response to pokeweed mitogen →		White *et al.*, 1975
			% /total IgB cells →	Rachelefsky *et al.*, 1976
			% /total EAC rosettes → (postdrug)	
				Shapiro *et al.*, 1976

TABLE 2 (CONTINUED)

			In Vitro	*In Vivo*	
Species	Sex/Strain	Drug	Concentration (μM)	Dose (mg/kg/day)/ Route/Duration of Exposure	Immunoglobulin Levels
Man	♂	Δ^9–THC in C Smoke		1–3/inhalation/ 28 days	
Man	♂	Δ^9–THC in C Smoke		1–3/inhalation/ 28 days	IgG ↓ IgM → IgD ↑ IgA →
Monkey	?/Rhesus	Δ^9–THC in C Smoke		up to 1/ inhalation/6 mo	IgG ↓ IgM ↓
Rat	♀/Fischer	Δ^9–THC		1–10/p.o./ 3–5 days	
Rat	♂, ♀/Fischer	Δ^9–THC		1–10/p.o./5 days	
		Δ^9–THC in C Smoke		0.7–4.0/inhalation /5 days	
Rat	♂, ♀/ Fischer	Δ^9–THC		6–12/p.o./ 5–26 days	
Rat	?/?	Δ^9–THC		100/i.p./ 5 days	
Mouse	?/Swiss Webster	Δ^9–THC		100/i.p./5 days	

Observations				
PFC[d]	Serum Anti-Body Titers	Mitogenicity	Enumeration of B-Cells	Reference
			EAC rosettes →	Cushman and Khurana, 1977
				Nahas *et al.*, 1979
		response to pokeweed mitogen trend ↓		Daul and Heath, 1975
direct pfc[h] response ↓	HT titer ↓			Rosenkrantz *et al.*, 1975a
direct pfc response ↓	HT titer ↓			Rosenkrantz, 1976
direct pfc response ↓	HT titer ↓			
direct pfc response ↓	HT titer ↓ HS titer ↓			Luthra *et al.*, 1980
	HT titer trend ↓			Ader and Grota, 1981
direct pfc response ↓				Lefkowitz and Chiang, 1975

TABLE 2 (CONTINUED)

			In Vitro	*In Vivo*	
Species	Sex/Strain	Drug	Concentration (μM)	Dose (mg/kg/day)/ Route/Duration of Exposure	Immunoglobulin Levels
Mouse	♂/BDF$_1$	Δ^9–THC		25–200/p.o./ >1 day	
		CBN, olivetol		25–200/p.o./ >1 day	
Mouse	♂/Balb/C	Δ^8–THC		60/i.p./ 1–5 days	
Mouse	♂/NYLAR -A	Δ^9–THC		25–200/p.o./ 1–16 days	
Mouse	♂/BDF$_1$	Δ^9–THC, CBD, CBN		25–100/i.p./ 1 day	
Mouse	?/?	Δ^9–THC		up to 200/p.o./ 6 days	
Mouse	♂/BDF$_1$	EHHC		25–200/i.p./1 day	
Mouse	♂/CD–1 immature	Δ^9–THC		1–10/i.p./4 days	
		CBD, CBN		25/i.p./4 days	
Mouse	♂/BDF$_1$	Δ^9–THC		10–25/i.p./ 8–10 days	

Observations				
PFC[d]	Serum Anti-Body Titers	Mitogenicity	Enumeration of B-Cells	Reference
direct pfc response delayed direct pfc response →				Levy *et al.*, 1975
direct pfc response ↓				Loveless and Munson 1976
	HT titer ↓	response to LPS mitogen ↓		Munson *et al.*, 1976
direct pfc response delayed				Levy and Heppner, 1981
direct pfc response ↓ delayed	HT titer ↓			Petersen and Lemberger, 1976
direct and indirect pfc response ↓				Klykken *et al.*, 1977
direct pfc response ↓	HT titer ↓			Zimmerman *et al.*, 1977
direct pfc response ↓	HT titer ↓			
direct pfc response ↓ reversible				Lefkowitz and Klager, 1978

TABLE 2 (CONTINUED)

			In Vitro	*In Vivo*	
Species	Sex/Strain	Drug	Concentration (μM)	Dose (mg/kg/day)/ Route/Duration of Exposure	Immunoglobulin Levels
Mouse	♂/BDF$_1$	Δ^9–THC	15–60		
Mouse	♂/BDF$_1$	Δ^9–THC		10–40/i.p./8 days	
Mouse	♂/BDF$_1$ immature/ mature	Δ^9–THC		25/i.p./5 days	
Mouse	♂/BDF$_1$	Δ^9–THC, Δ^8–THC		up to 100/i.p./ 1 day	
		1–CH_3– Δ^8–THC			
		abnor. Δ^8–THC			

Observations				
PFC[d]	Serum Anti-Body Titers	Mitogenicity	Enumeration of B-Cells	Reference
direct pfc response ↓				Lefkowitz and Klager, 1978
indirect pfc response ↓			B_1 rosettes ↓ B_2 rosettes	Lefkowitz *et al.*, 1978
indirect pfc response ↓	HT titer ↓		B_1 rosettes ↓ B_2 rosettes ↓	Pruess and Lefkowitz, 1978
direct pfc response ↓				Smith *et al.*, 1978

marked insult to the system of an organism must be sustained for at least several days before basal levels of immunoglobulins will be significantly reduced. In addition, one cannot, from an observation of reduced serum Ig levels, distinguish between inhibited synthesis or increased catabolism of these proteins. More sensitive tests whereby one can measure rates of antibody synthesis are assays that force an organism to respond to a specific antigen. Experiments in which these techniques were used are summarized below.

The hemolytic plaque (PFC) assay is used primarily in rodents to measure B-cell function. The animals are first immunized with an antigen (usually sRBC). Several days later the number of splenic, lymph node, or blood lymphocytes that can produce specific immunoglobulin against sRBC (or antigen-coated sRBC if another antigen was used to immunize the animals) is determined *in vitro* by counting the number of hemolytic plaques (areas of lysed erythrocytes) on an agar plate. The direct PFC assay determines the number of cells secreting IgM. The indirect assay, in which sRBC in combination with an anti-IgG serum are used, can detect the number of cells secreting IgG. The number of indirect plaques is determined by subtracting the number of direct plaques in plates lacking anti-IgG from the number of plaques in plates containing the antiserum.

Studies in which the PFC assay was employed after cannabinoid-treated rodents had been immunized with sRBC are listed in Table 2. Both the primary humoral (direct PFC) response and the secondary (indirect PFC) response to this antigen were inhibited in all studies. Δ^9–THC was found to be more potent than other nonpsychoactive natural cannabinoids such as CBD and CBN (Levy *et al.*, 1975; Zimmerman *et al.*, 1977), but less active than the synthetic nonpsychoactive cannabinoids 1–CH_3–Δ^8–THC, and abnormal Δ^8–THC (Smith *et al.*, 1978). Some authors have claimed that cannabinoid treatment did not attenuate the response of the IgM-secreting cells, but delayed its peak expression after immunization from day 4 to day 5 (Levy *et al.*, 1975; Petersen and Lemberger, 1976; Levy and Heppner, 1981). Others have observed an attenuated response on days 3–6 after immunization, with no increase in the latency of the response (Loveless and Munson, 1976; Klykken *et al.*, 1977; Smith *et al.*, 1978). Since the other groups of investigators assayed the response on one day only, one cannot ascertain from their data whether the response was attenuated or merely delayed. Levy and Heppner (1980) do not consider a drug immunosuppressive if the response is delayed but not reduced in overall magnitude. On the other hand, it can be argued that a 24–48 hr delay in the formation of circulating antibodies to a pathogen could allow for increased proliferation of the pathogen in the interim, and thus alter the outcome of the host-pathogen interaction in favor of the pathogen.

There are apparent differences in sensitivity to the inhibitory effects of the cannabinoids as measured by the PFC response. Immature mice are more sensitive than mature mice, responding with 50% inhibition of the direct response at doses of Δ^9–THC as low as 5 mg/kg (Zimmerman *et al.*, 1977) as compared with 75 mg/kg for adult mice (Smith *et al.*, 1978). Although this difference might have been due to strain differences, Pruess and Lefkowitz (1978) found that immature (4-wk-old) mice responded with an inhibited indirect PFC response to a dose of 25 mg/kg Δ^9–THC, while 14-wk-old mice exhibited no effect. They speculated that age-related differences in cell membranes or in the pharmacokinetics of the drug were responsible for the differential effects. Adult rats also appear to be more sensitive than adult mice. Rosenkrantz *et al.* (1975a), Rosenkrantz (1976) and Luthra *et al.* (1980) were able to elicit dose-related significant effects at oral and inhaled doses of less than 10 mg/kg Δ^9–THC. The disparity is greater than the expected two-fold difference in sensitivity calculated on the basis of the rat:mouse body surface area ratio (Freireich *et al.*, 1966). Luthra *et al.* (1980) also demonstrated, by varying the days when Δ^9–THC was administered relative to the immunization with sRBC, that in the rat, the inductive phase of antibody formation (i.e., the early stage during which the antigen is being processed by the macrophages and presented to the B-cells) is more affected by the drug than the productive phase when the antibodies are actively secreted. Lefkowitz and Klager (1978), by testing the *in vitro* PFC response to sRBC in groups of mice sacrificed either immediately after subchronic treatment with Δ^9–THC or after a 7-day drug-free recovery period, demonstrated that the drug effect was reversible.

Serum antibody titers (both hemagglutination titer (HT) and hemolysin titer (HS)) against the antigen sRBC are also a direct measure of antibody secretion and have been assayed by determining the highest dilution of serum from immunized cannabinoid-treated animals causing agglutination or lysis respectively of sRBC (Table 2). All groups of investigators found a decrease in HT titer that paralleled the decrease in number of direct or indirect PFC. Luthra *et al.* (1980) also found a decrease in HS titer. In a brief letter, Ader and Grota (1981) stated that they were able to produce only a slight decrease in HT titer six days after immunization with sRBC in rats treated subacutely with 100 mg/kg Δ^9–THC. When Δ^9–THC was combined with cyclophosphamide, however, the suppression of humoral immunity was greater than had been achieved by either drug alone. Although preliminary, these results raise the question of possible detrimental drug interactions when patients undergoing immunomodulating chemotherapy are treated with cannabinoids for the relief of nausea and vomiting.

The mechanism underlying the cannabinoid-induced inhibition of humoral immunity is not well understood. Smith (1979) found that the effect of Δ^9–THC was the same in groups of adrenalectomized and sham-operated mice, suggesting that the response was not secondary to a drug-induced release of corticosteroids. In a further experiment, she demonstrated that in mice immunized with the T-independent antigen LPS instead of the T-dependent sRBC, a dose of 200 mg/kg 1–CH_3–Δ^8–THC had virtually no effect on the PFC response. She therefore suggested that this cannabinoid acted by suppressing T_H cells or activating T_S cells instead of affecting the B-cells directly.

Antigenicity of Cannabinoids

In 1971, Tennant *et al.* and Liskow *et al.* described allergic manifestations that were apparently exacerbated in patients who smoked cannabis (Table 3). Tennant *et al.* (1971) demonstrated that several of their 10 subjects reacted to skin testing with common allergens such as ragweed or house dust, but none reacted to patch-testing with an ether extract of hashish. Agar-gel diffusion studies using the serum from four of the subjects and the extract were also negative. These authors concluded that hashish was probably not the primary allergen but its use may have potentiated allergic tendencies in their patients. A similar picture of negative skin tests to cannabinoids was reported among 63 randomly selected marihuana users by Lewis and Slavin (1975) even though three of the subjects stated that they experienced allergic symptoms after marihuana smoking. Seven subjects showed skin reactivity to “hemp,” but had no history of marihuana-related allergies. The authors concluded that allergic reactions to marihuana were rare and were not related to skin reactivity.

On the other hand, Liskow *et al.* (1971) were able to demonstrate positive reactions to scratch tests with cannabis extracts in a subject who reported experiencing allergic symptoms that were temporally related to cannabis use. A passive transfer study (in which the subject’s serum is injected into the skin of a nonallergic individual who is then tested for reaction to the allergen) was performed to prove that the response was indeed immunological (i.e., not caused by nonspecific irritation). The results indicated that Δ^9–THC, CBD and CBC, as well as the extract, could provoke an allergic reaction. These results were confirmed by Shapiro *et al.* (1974, 1976) who also demonstrated the presence of specific antibodies to Δ^9–THC, Δ^8–THC, CBN, and CBD in all of a group of 34 experienced marihuana users by means of standard passive hemagglutination and the indirect Coombs tests. Prior absorption of six of these

Coombs positive sera with cannabis extract or individual cannabinoids removed the specific antibodies to those cannabinoids.

In animals, antibody formation to Δ^9–THC has also been demonstrated. This process was suspected to be occurring when spontaneously hypertensive rats failed to become tolerant to the hypotensive effects of Δ^9–THC while being treated with the immunosuppressant, azathioprine (Nahas *et al.*, 1973b). This suggested that when tolerance did develop, it was due to the formation of anti-Δ^9–THC antibodies. Guinea pigs sensitized to Δ^9–THC reacted strongly when Δ^9–THC was applied to their hindquarters 15 days later. The presence of specific circulating antibodies to Δ^9–THC was confirmed by the observation of an increase in the degranulation of peritoneal mastocytes in the presence of sensitized guinea pig serum and Δ^9–THC (Lecorsier *et al.*, 1977).

Thus it appears that cannabinoids can elicit the formation of specific antibodies in both humans and experimental animals. The drug or a metabolite is probably acting as a hapten, combining with a protein to form an antigenic complex. These complexes can also be made *in vitro*. Antibodies to Δ^9–THC have been produced by immunizing rabbits and sheep with conjugates of THC and albumin (Marks and Teale, 1979). This was done to enhance antibody formation in the development of a radioimmunoassay for cannabinoids in biological fluids. Δ^9–THC-albumin conjugates have also been used to immunize rodents against Δ^9–THC. When subsequently challenged with Δ^9–THC, immunized rats showed an attenuated response to the effects of this drug on spontaneous motor activity (Strahilevitz *et al.*, 1974). Similarly, immunized mice were far less sensitive than control mice to Δ^9–THC-induced prolongation of pentobarbital sleeping time (Giusti *et al.*, 1980). The latter investigators were subsequently able to demonstrate the passive transfer of the specific anticannabinoid antibody by observing a similar loss of sensitivity to the same drug effect in mice treated with an anti-Δ^9–THC serum prepared in immunized rabbits (Chiarotti *et al.*, 1980). Several of these investigators (Nahas *et al.*, 1973b; Strahilevitz *et al.*, 1974; Giusti *et al.*, 1980) have discussed the role that antibody formation may play in the development of tolerance to the effects of Δ^9–THC. This topic will be discussed in Section 6.

Effects on Cell-Mediated Immunity

As described in Section 2, cell-mediated immunity is dependent on the function of several subpopulations of T-cells, the macrophages, and the null cells. The integrity and function of the cell-mediated immune system can be studied by a variety of approaches. T-cells and their subpopulations in blood and other lymphoid tissues can be enumerated. Their ability to undergo blast transformation and secrete lymphokines

TABLE 3

Antigenicity

Species	Sex (no. of Ss)/ Strain	Drug	Dose (mg/kg)/ Route/ Exposure	Allergic Reactions
Man	♀ (1 S)	Δ^9–THC in C[a] smoke	?/inhalation/ 2 times	+[b]
Man	♂ (10 Ss)	Δ^9–THC in C smoke	?/inhalation/ heavy	+
Man	♂, ♀ (17 Ss)	Δ^9–THC in C smoke	?/inhalation/ 1/mo–1/day	
Man	⛢ (34 Ss)	Δ^9–THC in C smoke	?/inhalation/ > 20 times	
Man	? (63 Ss)	Δ^9–THC in C smoke	?/inhalation/ ?	3/63 +
Guinea pig	?/Hartley	Δ^9–THC	2.5 mg/kg/ s.c./8 days	

a) cannabis b) positive reaction c) negative reaction d) crude cannabis extract

Observations		
Skin Testing	Antibody Formation	Reference
Δ^9-THC + Δ^8-THC —[c] CBD + CBC + CBN —	+ (passive transfer study)	Liskow *et al.*, 1971
hashish extract -	— (agar-gel diffusion)	Tennant *et al.*, 1971
	15/17 + (indirect Coombs test)	Shapiro *et al.*, 1974
	—34/34 + (indirect Coombs test) —serological reactivity to Δ^9-THC, Δ^8-THC, CBN, CBD	Shapiro *et al.*, 1976
Δ^9-THC all — Δ^8-THC 1/63 + CCE[d] all — C leaf 7/63 +		Lewis and Slavin, 1975
90% + (Modified Magnusson test)	70% of animals strong + (mastocyte degranulation)	Lecorsier *et al.*, 1977

can be tested *in vitro*. Finally, their function can be assessed *in vivo* by the elicitation of the DTH response. Evidence related to cannabinoid-induced effects on cell-mediated immunity will be described in this section.

Effects on T-cells

Enumeration of T-cells: The surfaces of T-cells from humans and some other animals contain specific receptors for sRBC. Thus T-cells can be distinguished from other lymphocytes by their ability, under certain conditions, to bind and form rosettes with sRBC. T-cells can also be identified by staining with fluorescein-conjugated heterosera prepared against thymus or brain which have been made T-cell specific by previous removal of B-cell-reactive antibodies by absorption with B-cells.

Studies of the effects of cannabinoids in which the enumeration of T-cells was included are listed in Table 4, and there are considerable inconsistencies in the results. While the number of T-cells spontaneously forming rosettes with sRBC has been reported to be abnormally low in small samples of presumably drug-free chronic users (Petersen *et al.*, 1975, 1976) and transiently depressed in two of three subjects after acute exposure to cannabis (Petersen *et al.*, 1976), other investigators (Kaklamani *et al.*, 1978) have found normal proportions and absolute numbers of spontaneous E-rosettes in heavy users of hashish both before and after acute exposure to the drug. McDonough *et al.* (1980) found that an opioid-induced naloxone-reversible reduction in the percentage of spontaneous T-rosettes in street opiate addicts was independent of self-reported cannabis use. In this group, however, cannabinoids may have been unable to impair further a response that was already maximally inhibited. Since the controls were drawn from institute staffs and presumably did not use illicit drugs, this possibility cannot be assessed. Rachelefsky *et al.* (1976) studied a group of moderate and heavy marihuana users before, during, and after 64 consecutive days of experimental administration of marihuana. The number of T-cells forming rosettes was initially depressed in the smokers during the baseline drug-free period, but returned to normal during the smoking period. The authors suggested that factors other than marihuana accounted for this observation. In all of the above studies, the total number of T-lymphocytes (i.e., those forming rosettes after incubation overnight at 4°C) was assessed. The basic problem with this technique is that it enumerates the total of at least four subpopulations of T-cells, and therefore may not be sensitive to effects on one subpopulation only.

The observation that 9 of 23 chronic marihuana users had an abnormally low number of T-lymphocytes that formed "active" rosettes (Gupta *et al.*, 1974; Cushman *et al.*, 1975) stimulated additional research by this group. Expansion of the study group to 35 young men and women who smoked marihuana at least once weekly and 34 nonuser controls (Cushman and Khurana, 1976) confirmed that the percentage of lymphocytes forming early "active" rosettes after incubation with sRBC for one hour at 37°C was significantly lower in the users than in the controls. The total percentages of T-cells forming rosettes after incubation overnight at 4°C were similar in the two groups. Similar effects were subsequently observed in a group of users during a four-week period of experimental marihuana administration (Cushman and Khurana, 1977). The percentage of early rosettes had not fully recovered to baseline values at two weeks postdrug.

In vitro exposure of lymphocytes of nonusers to cannabinoids also resulted in a decrease in the percentage of early T-rosettes, with no change in the percentage of total rosettes (Cushman, 1976). Δ^9–THC, CBN, and CBD appeared to be equipotent in producing this effect. A less marked decrease was observed when lymphocytes obtained from marihuana users were incubated with Δ^9–THC, probably because their ability to form early rosettes was already almost maximally inhibited. Since only the highest concentrations of Δ^9–THC caused any reduction in the number of sRBC attached to each rosetting lymphocyte, Cushman (1976) suggested that the inhibitory action was not due to Δ^9–THC occupation of receptor sites, but rather to Δ^9–THC-induced changes in cell membrane properties.

These results suggest that a subpopulation of early reactive lymphocytes is particularly sensitive to the effects of the cannabinoids. A similar selective decrease in the percentage of early "active" rosettes has been described in certain disease states including lepromatous leprosy (Nath *et al.*, 1974), solid tumors, lymphomas, and viral diseases (Wybran and Fudenberg, 1973). These lymphocytes appear to differ from those forming late rosettes in their membrane chemistry and distribution of sRBC receptors (Yu, 1975).

T-cells have also been enumerated in animals treated with cannabinoids. Lefkowitz *et al.* (1978) and Pruess and Lefkowitz (1978) observed decreases in the percentage of splenic lymphocytes forming T-rosettes in mice treated for seven days with up to 40 mg/kg Δ^9–THC. Again, immature mice were more sensitive to the effects of the drug than mature mice (Pruess and Lefkowitz, 1978). Smith (1979) determined the percentage of T-lymphocytes in the spleen, thymus, and lymph nodes of mice treated with 200 mg/kg 1–CH_3–Δ^8–THC by means of the direct immunofluorescence technique described above. The percentage of

TABLE 4

Cellular Immunity: Enumeration of T Cells

			In Vivo	*In Vitro*
Species	Sex/Strain	Drug	Dose (mg/kg)/ Route/Duration of Exposure	Concentration (μM)
Man	♂, ♀ (35 Ss)	ΔΔ^9-THC in C[a]Smoke	?/inhalation/ ⩾ 1 wk for ⩾ 1 yr	
Man	♂, ♀ users and nonusers	Δ^9-THC, CBN, CBD, olivetol		0.01–3,000
Man	♂ (10 Ss) moderate and heavy users	Δ^9-THC in C Smoke	1–3/inhalation/ 28 days	
Man	♂ (13 Ss) moderate and heavy users	Δ^9-THC in C Smoke	?/inhalation/ > 1 yr	

a) cannabis b) decrease c) no change

Method	Observation	Reference
early "active" E rosettes	% ↓[b]	Cushman and Khurana, 1976
late E rosettes (WHO method)	% ↓	
cold enhanced WHO method	% →[c]	
early "active" E rosettes	% ↓ (most marked in nonusers)	Cushman, 1976
late E rosettes (cold enhanced WHO method)	% →	
early "active" E rosettes	% ↓ (reversible)	Cushman and Khurana, 1977
late E rosettes (cold enhanced WHO method)	% →	
spontaneous E rosettes	% ↓	Petersen *et al.*, 1975

TABLE 4 (CONTINUED)

			In Vivo	*In Vitro*
Species	Sex/Strain	Drug	Dose (mg/kg)/ Route/Duration of Exposure	Concentration (μM)
Man	♂ (13 Ss) moderate and heavy users	Δ^9–THC in C Smoke	0.14/inhalation/ acute	
Man	♂(12 Ss) moderate and heavy users	Δ^9–THC in C Smoke	$\geqslant$ 0.3/inhalation/ 63 days	
Man	♂(12 Ss) heavy users	Δ^9–THC in C Smoke	~5/inhalation/ acute	
Mouse	♂/BDF_1	Δ^9–THC	10–40/i.p./ 7 days	
Mouse	♂/BDF_1 mature/ immature	Δ^9–THC	25/i.p./ 7 days	
Mouse	♀/CDF_1	1–CH_3– Δ^8–THC	200/i.p./acute	

Method	Observation	Reference
spontaneous E rosettes	% ↓ (reversible)	Petersen *et al.*, 1976
spontaneous E rosettes	predrug % ↓ (9 days drug-free) total ↓	Rachelefsky *et al.*, 1976
	during treatment % → total →	
spontaneous E rosettes	predrug % → (20 hr drug-free) total →	Kaklamani *et al.*, 1978
	postdrug % → total →	
T_1 E rosettes (spleen)	total ↓	Lefkowitz *et al.*, 1978
T_2 E rosettes (spleen)	total ↓	
E rosettes (spleen)	total ↓ (most marked in immature animals)	Pruess and Lefkowitz, 1978
direct immunofluorescence	% (spleen) → % (thymus) ↓ % (lymph node) →	Smith, 1979

T-cells was reduced only in the thymus. Mice immunized with sRBC demonstrated no change in the percentage of T-cells in any organ.

Although the results described are conflicting, it is possible that cannabinoids are affecting some subpopulations of T-cells. Newer techniques for selective enumeration that involve the preparation of specific antisera against various alloantigens present on the surface of different subpopulations of T-cells could be used to extend our knowledge of the effects of cannabinoids on these cells.

In Vitro Measures of T-Cell Function: Response to Lymphocyte Mitogens and Allogeneic Cells: More valuable than the simple enumeration of T-lymphocytes are indicators of their function both *in vitro* and in the intact organism. Studies of the *in vitro* response to mitogens and allogeneic cells can reveal drug-induced changes in their ability to respond to stimulation (blastogenesis), to secrete lymphokines, and to kill allogeneic cells.

Investigations of the effects of cannabinoids on *in vitro* T-lymphocyte function are listed in Table 5. The blastogenic response of T-lymphocytes exposed to cannabinoids either *in vivo* or *in vitro* is usually assessed by estimating the amount of DNA synthesis from the incorporation of radiolabeled thymidine into the acid-insoluble fraction of cells stimulated with the plant lectins phytohemagglutinin (PHA), concanavalin A (Con A), or pokeweed mitogen (PWM) or allogeneic cells such as mixed lymphocyte cultures (MLC). Different mitogens are believed to stimulate different subpopulations of T-cells (Sharma, 1982). For example, PHA appears to stimulate mature T-cells, Con A, immature cells, and PWM, both T-cells and B-cells. The MLC can be used to evaluate the general responsiveness of T-cells, and the process is believed to be macrophage-dependent.

The earliest reports of a cannabis-induced effect on T-cell function were those of Nahas *et al.* (1973a, 1974c) who observed a decreased response to both PHA and MLC in the peripheral lymphocytes of 51 moderate and heavy marihuana users. The blastogenic response was reported as being closer to that observed in a group of immunosuppressed patients than to that in a control group of healthy nonusers. A similar trend was observed in some of a group of 13 users studied both before and after acute exposure to marihuana (Petersen *et al.*, 1975, 1976). Other investigators, however, have been unable to confirm these findings in small groups of moderate or heavy users either using the drug illicitly (White *et al.*, 1975) or as part of a clinical experiment (Rachelefsky *et al.*, 1976). Two groups even reported a slight stimulation of T-cell responsiveness (Lau *et al.*, 1976; Kaklamani *et al.*, 1978).

The same inconsistency in T-cell response to mitogens has appeared when the effects of *in vitro* exposure to cannabinoids have been studied. In a series of papers, one group of investigators has reported a consistent inhibition of the synthesis of macromolecules (DNA, RNA, and protein) in human lymphocytes exposed to a variety of cannabinoids (Nahas *et al.*, 1974a and b, 1975, 1976a and b, 1977; Desoize and Nahas, 1976; Desoize *et al.*, 1976, 1979a and b; Banchereau *et al.*, 1979). Active substances included Δ^9–THC and Δ^8–THC, 11–OH–Δ^9–THC, CBD, CBN, CBCh, and CBC, while olivetol was less potent. The concentration of cannabinoids required to inhibit blastogenesis by 50% ranged from 3.5–16 μM and was directly correlated with the concentration of α_1–lipoprotein in the incubation medium. This protein binds Δ^9–THC, and probably affected the concentration of the free drug to which the cells were exposed (Banchereau *et al.*, 1979). The inhibition was reversible when the cells were washed (Desoize and Nahas, 1976). On the basis of precursor uptake experiments, Desoize *et al.* (1979a and b) concluded that Δ^9–THC, because of its lipid solubility, may produce a nonspecific alteration of the membrane configuration which would inhibit the function of the membrane-bound transport systems (see Section 7). Other psychoactive drugs including diazepam, chlordiazepoxide, imipramine, phenytoin, haloperidol, and phenobarbital also inhibited the uptake of radiolabeled thymidine (Banchereau *et al.*, 1979).

On the other hand, Rachelefsky and Opelz (1977) were unable to detect any change in the *in vitro* response of normal human lymphocytes to PHA or MLC in the presence of up to 106 μM Δ^9–THC. The reason for these inconsistencies is unclear but may be related to different experimental conditions such as the concentrations of mitogens and serum proteins in the culture media and the incubation period of the cultures.

The results of animal experiments are more in agreement than those of the human studies (Table 5). A decreased blastogenic response to mitogens as reflected by decreased incorporation of radiolabeled thymidine has been demonstrated in monkeys treated for six months with up to 1 mg/kg Δ^9–THC per day in cannabis smoke (Daul and Heath, 1975) and in mice treated with 25–200 mg/kg Δ^9–THC for 1–16 days (Munson *et al.*, 1976; Pruess and Lefkowitz, 1978). Again the latter group demonstrated that immature mice were more sensitive to the drug than mature animals. *In vivo* treatment of sRBC-sensitized mice with 200 mg/kg 1–CH_3–Δ^8–THC did not alter the responsiveness of the lymph node T-lymphocytes to PHA and enhanced the responsiveness of the spleen T-cells (Smith, 1979). The author suggested that the drug may have been suppressing a splenic factor which normally inhibits T-cell proliferation.

In vitro exposure of rat splenic lymphocytes to Δ^9–THC concentrations of 1.6–22.4 μM also decreased the responsiveness of these cells to

TABLE 5

Cellular Immunity: Response to Lymphocyte Mitogens and Allogeneic Cells

				In Vitro	*In Vivo*
Species	Sex (no. of Ss)/ Strain	Source	Drug	Concentration (μM)	Dose (mg/kg)/ Route/ Duration of Exposure
Man	?/(51 Ss) moderate and heavy users	peripheral blood	Δ^9–THC in C[a] Smoke		?/inhalation/ >1 yr
Man	?(?)	peripheral blood	Δ^9–THC, Δ^8–THC, 11–OH–Δ^9–THC, CBD, CBN, CBCh, CBC, olivetol	10–1,000	
Man	?(?)	peripheral blood	Δ^9–THC, CBD olivetol derivatives	1–100	

a) cannabis b) decrease c) no change d) increase

		T-Cell Function		
Mitogen	Allogeneic Cells	^{3}H–Thymidine Incorporation	Other	Reference
PHA		↓[b]		Nahas *et al.*, 1973a
	MLC	↓		Nahas *et al.*, 1974c
PHA		↓	^{3}H–uridine incorp ↓	Nahas *et al.*, 1974a and b
			^{3}H–leucine incorp ↓	Nahas *et al.*, 1975
	MLC	↓	^{3}H–uridine incorp ↓	Nahas *et al.*, 1976a and b
			^{3}H–leucine incorp ↓	Nahas *et al.*, 1977
PHA		↓	^{3}H–uridine incorp ↓	Desoize and Nahas, 1976
			^{3}H–leucine incorp ↓	Desoize *et al.*, 1976
			^{14}C–amino-isobutyric acid incorp ↓	Desoize *et al.*, 1979a and b
			^{3}H–thymidine uptake ↓	

TABLE 5 (CONTINUED)

				In Vitro	*In Vivo*
Species	Sex (no. of Ss)/ Strain	Source	Drug	Concentration (μM)	Dose (mg/kg)/ Route/ Duration of Exposure
Man	♂, ♀(12 Ss) moderate and heavy users	peripheral blood	Δ^9–THC in C Smoke		?/inhalation/ ⩾1 yr
Man	♂(13 Ss) moderate and heavy users	peripheral blood	Δ^9–THC in C Smoke		?/inhalation/? 0.15/ inhalation/ acute
Man	♂(12 Ss) moderate and heavy users	peripheral blood	Δ^9–THC in C Smoke		> 0.3/ inhalation/ 64 days
Man	?(?)	peripheral blood	Δ^9–THC	60–106	
Man	♂(8 Ss) heavy users	peripheral blood	Δ^9–THC in CCE		3/ inhalation/ 18 days
Man	♂(12 Ss) heavy users	peripheral blood	Δ^9–THC in C Smoke		3/ inhalation/ acute
Man	?(?)	peripheral blood	Δ^9–THC	10–470	
Monkey	?/Rhesus	peripheral blood	Δ^9–THC in C Smoke		up to 1/ inhalation/ 6 mo

		T-Cell Function		
Mitogen	Allogeneic Cells	^{3}H-Thymidine Incorporation	Other	Reference
PHA		→[c]		White *et al.*, 1975
pokeweed		→		
PHA			% stimulated ↓ (trend)	Petersen *et al.*, 1975
PHA			% stimulated transient ↓ (3 Ss)	Petersen *et al.*, 1976
PHA		→		Rachelefsky *et al.*, 1976
	MLC	→		
PHA		→		Rachelefsky and Opelz, 1977
	MLC	→		
PHA		↑[d](trend)		Lau *et al.*, 1976
PHA		→		Kaklamani *et al.*, 1978
PHA		↓	^{14}C-uridine incorp ↓	Banchereau *et al.*, 1979
PHA		↓		Daul and Heath, 1975
pokeweed		↓		
Con A		↓		

TABLE 5 (CONTINUED)

				In Vitro	*In Vivo*
Species	Sex (no. of Ss)/ Strain	Source	Drug	Concentration (μM)	Dose (mg/kg)/ Route/ Duration of Exposure
Guinea pig	?/?	peritoneal exudate	Δ^9–THC		0.8/?/acute
		lymph node	Δ^9–THC	40	
Rat	?/?	spleen	Δ^9–THC	1.6–22.4	
Rat	♀/Wistar	peritoneal exudate	Δ^9–THC		0.3–1.3/ i.p./acute
Mouse	♂/NYLAR–A	spleen	Δ^9–THC, CBN, olivetol		25–200/p.o./ >1 day
Mouse	♂/NYLAR–A	spleen	Δ^9–THC		25–200/p.o./ 1–16 days
Mouse	?/?	spleen	Δ^9–THC, Δ^8–THC, CBG, CBN, olivetol	0.1–10	
Mouse	♂/?	spleen	Δ^9–THC	0.1–10	

	T-Cell Function			
Mitogen	Allogeneic Cells	^{3}H–Thymidine Incorporation	Other	Reference
			MIF activity ↓	Mellors, 1976
Con A			MIF activity ↓	
PHA		↓		Nahas *et al.*, 1974a
			MIF activity ↓	Gaul and Mellors, 1975
	P-815 mastocytoma cells		destruction of target cells (^{51}Cr release) ↓	Levy *et al.*, 1975
PHA		transient ↓		Munson *et al.*, 1976
Con A			lysolecithin acyltransferase activity ↓	Greenberg *et al.*, 1977
Con A			lysophosphatidylcholine acyltransferase activity ↓	Greenberg and Mellors, 1978

TABLE 5 (CONTINUED)

				In Vitro	*In Vivo*
Species	Sex (no. of Ss)/ Strain	Source	Drug	Concentration (μM)	Dose (mg/kg)/ Route/ Duration of Exposure
Mouse	♂/BDF_1 mature/ immature	spleen	Δ^9–THC		25/i.p./ 5 days

stimulation with PHA (Nahas *et al.*, 1974a). This result is in agreement with the work on human lymphocytes published by the same group.

T-lymphocyte function has also been assessed by measuring the ability of these cells to secrete lymphokines or to kill allogeneic cells. A decrease in MIF activity has been demonstrated in cells harvested from the peritoneal exudates of rats (Gaul and Mellors, 1975) and guinea pigs (Mellors, 1976) treated acutely with Δ^9–THC at doses in the range of 1 mg/kg and immunized with Freund's adjuvant. A similar decrease in secretion of MIF was observed in Con A-stimulated cultures of lymph node lymphocytes exposed to 40 μM Δ^9–THC (Mellors, 1976). Levy *et al.* (1975) treated mice with up to 200 mg/kg Δ^9–THC or other cannabinoids. Splenic lymphocytes from these animals demonstrated a decreased ability to kill allogeneic P–815 mastocytoma cells as evidenced by a decreased release of ^{51}Cr from the target cells. This assay is specific for the T_K cell. All of these observations point to a cannabinoid-induced impairment of T-cell function.

The fact that cannabinoids can affect blastogenesis and other manifestations of T-cell function in several species of animals suggests that the same effects could occur in humans given sufficient exposure to

	T-Cell Function			
Mitogen	Allogeneic Cells	^{3}H–Thymidine Incorporation	Other	Reference
PHA		↓ (immature mice)		Pruess and Lefkowitz, 1978

the substances. The reason that some laboratories have observed effects in cannabis users and others have not is still unclear at this time.

In Vivo Assessment of T-Cell Function: Delayed-Type Hypersensitivity: The delayed cutaneous hypersensitivity response is dependent on the function of a number of components of the cell-mediated system including the T_{DTH}-lymphocytes, the macrophages, as well as on an intact inflammatory response. Its elicitation is, therefore, a demonstration of the functional capacity of the cell-mediated immune system. This reaction can be stimulated by the topical application or intradermal injection of a variety of bacterial or chemical sensitizing agents in previously sensitized humans and experimental animals.

The delayed cutaneous hypersensitivity response has been studied in cannabinoid-exposed humans and animals (Table 6). Gupta *et al.* (1974) found that only 69% of their cannabis-smoking subjects responded to one or more of four common recall antigens (mumps, tuberculin, trichophyton, and candida) but that the response was not correlated with the decrease in the percentage of "early" active T-rosettes discussed above. Although this percentage of responders is lower than would be expected in the general population, the number of subjects is

TABLE 6

Cellular Immunity: Delayed Cutaneous Hypersensitivity Response

Species	Sex (no. of Ss)/ Strain	Drug	Dose (mg/kg)/ Route/Duration of Exposure
Man	♂, ♀(23 Ss) moderate and heavy users	Δ^9–THC in C[a] smoke	?/inhalation/ >1 yr
Man	♂(34 Ss) moderate and heavy users	Δ^9–THC in C smoke	?/inhalation/ ≥6 mo
Mouse	♂/NYLAR–A	Δ^9–THC	25–200/p.o./ 1–25 days
Mouse	♀/CDF_1	Δ^8–THC, 1–CH_3–Δ^8–THC, abnor. Δ^8–THC	75/i.p./3 days
Mouse	♂/CDF_1	EHHC	25–100/i.p./ acute
Mouse	♂/BDF_1	Δ^9–THC, Δ^8–THC, 1–CH_3–Δ^8–THC, abnor. Δ^8–THC	1–100/s.c./ 4 days
Mouse	?/Balb/C	Δ^9–THC in CCE, Δ^9–THC, 1–CH_3–Δ^8–THC	up to 200/ s.c./3 days

a) cannabis b) positive response c) increase d) decrease

Sensitizing Agent	Observation	Reference
4 recall antigens	69% +[b] response	Gupta *et al.*, 1974
DNCB 4 recall antigens	100% + response 94% + response to ≥1 antigen	Silverstein and Lessin, 1976
skin grafts from BDF_1 mice	graft survival ↑[c]	Munson *et al.*, 1976
oxazolone	DTH response ↓[d]	Smith *et al.*, 1976
C. parvum	DTH response ↓	Klykken *et al.*, 1977
sRBC	DTH response ↓	Smith *et al.*, 1978
sRBC	DTH response ↓	Morahan *et al.*, 1979

low (16), and no controls were included. The results, therefore, are difficult to assess. Silverstein and Lessin (1976) observed a 94% response rate to one or more of four common antigens (mumps, varidase, tuberculin, and candida). This group also observed a 100% response to the strong allergen 2,4-dinitrochlorobenzene (DNCB) as compared with an 80% response rate in an age-matched group of cancer patients. A decreased response to recall antigens or DNCB has been related to a less favorable prognosis in cancer patients (Eilber and Morton, 1970). Since the degree of response to these antigens is difficult to quantitate in humans, these tests may not be sufficiently sensitive to detect subtle changes in the cell-mediated immune system.

A number of studies from one laboratory have established that when given in sufficient doses, cannabinoids can attenuate the delayed cutaneous hypersensitivity response in mice challenged with oxazolone (Smith *et al.*, 1976), sRBC (Smith *et al.*, 1978; Morahan *et al.*, 1979), and *Corynebacterium parvum* (Klykken *et al.*, 1977). A number of psychoactive cannabinoids (Δ^9-THC, Δ^8-THC) and nonpsychoactive synthetic analogs (1-CH_3-Δ^8-THC, abnormal Δ^8-THC) were active at doses as low as 1 mg/kg given s.c.

The length of time required for the rejection of skin transferred from a donor to a genetically different recipient of the same species is also an indicator of T-cell function. Munson *et al.* (1976) reported a significantly increased graft survival time in mice treated with 25 mg/kg Δ^9-THC or more. The increase in graft survival time was roughly equivalent in mice treated with 200 mg/kg Δ^9-THC and those given 25 mg/kg 6-mercaptopurine.

The mechanism underlying the reduced DTH response is not known. Smith (1979) found that spleen cells from sensitized mice treated with 1-CH_3-Δ^8-THC were able to elicit a reaction to sRBC when transferred to unsensitized mice. Therefore the T-cells were intact, sensitized, and capable of a response. When spleen cells from a sensitized untreated mouse were transferred to a drug-treated animal, the DTH response was reduced by 50%, i.e., the same degree of inhibition observed in sensitized mice treated with drug directly. Cannabinoids did not inhibit the inflammatory response as measured by the carrageenin-induced footpad inflammation test (Smith *et al.*, 1978). It appeared then that the drug was acting on accessory cells (T_S, T_H, or macrophages) that modulate the reaction, or on other factors necessary for its expression. In mice, this response seems to be more sensitive to the effects of cannabinoids than many other immune system parameters. Since the severity of this reaction can be quantitated more accurately in animals than in humans, these experiments may be the most sensitive indicators of subtle drug-induced effects.

In summary, a decreased delayed cutaneous hypersensitivity response has not been demonstrated in human marihuana smokers, but is evident in mice treated with behaviorally relevant doses of Δ^9–THC or with other cannabinoids.

Effects on Macrophages and Other Cells

Macrophage function and status after exposure to toxic agents can be assessed by evaluating the morphology and number of cells (i.e., leukocyte differential), and/or their function both *in vivo* and *in vitro* (chemotaxis, specific and nonspecific phagocytosis, and bactericidal, tumoricidal, and tumoristatic activities). In addition, markers of metabolic activity such as oxygen consumption, superoxide formation, and enzyme activities can be assessed.

A number of investigators have studied macrophage structure and function after exposure to cannabis smoke or pure cannabinoids both *in vivo* and *in vitro* (Table 7). In humans who had been heavy users of cannabis for at least two years, the alveolar macrophages obtained by means of bronchopulmonary lavage demonstrated ultrastructural abnormalities (Mann *et al.*, 1971; Davis *et al.*, 1980). The former group reported abnormal needle-shaped inclusions and pale areas within inclusions in the macrophages of these users, a lower than normal percentage of macrophages in the recovered cells, and increased glass adherence, interpreted as a difference in net negative surface charge. Mean cell diameter and phagocytosis of heat-killed *Candida albicans* were normal. Davis *et al.* (1980) reported an increase in the total number of recovered macrophages and bizarre changes in the surface features that were seen in 50% of the cells and were characterized by large globular projections, loss of ruffling, surface bleb formation, and the development of blunt villi.

In vivo exposure to pure Δ^9–THC did not alter the percentage of macrophages recovered from rat peritoneal exudates or their viability (Gaul and Mellors, 1975). The ability of reticuloendothelial (Kupffer) cells to phagocytize colloidal carbon was unchanged in mice treated with up to 200 mg/kg Δ^9–THC (Munson *et al.*, 1976). *In vitro* exposure of rat alveolar macrophages to concentrations of pure Δ^9–THC up to 100 μM has produced decreased cell motility and release of β-glucuronidase and increased cytolysis in hypotonic solutions (Chari-Bitron, 1976). Similar treatment produced increased formation of autophagic vacuoles in mouse peritoneal macrophages (Raz and Goldman, 1976).

More dramatic effects have been demonstrated after *in vivo* or *in*

TABLE 7

Cellular Immunity: Macrophages

				In Vitro
Species	Sex/Strain	Source	Drug	Concentration (μM)
Man	♂, ♀	broncho-pulmonary lavage	C[a]Smoke	
Man	?	broncho-pulmonary lavage	C Smoke	
Rat	♀/Wistar	peritoneal exudate	Δ^9–THC	
Rat	?/?	lung homogenate	C Smoke whole/ gas phase fresh/ stale	
Rat	?/?	broncho-pulmonary lavage ?	Δ^9–THC	10–100
Rat	♂/CD	broncho-pulmonary lavage	C Smoke whole/ gas phase fresh/ stale	2–6 ml smoke

a) cannabis b) decrease c) no change d) increase

In Vivo		
Dose/Route/Duration of Exposure	Observation	Reference
?/inhalation/ ≥2 cigarette-yr	—% macrophages ↓[b] —mean cell diameter →[c] —no. of multinucleate cells → —ultrastructural morphology (abnormal inclusions) ↑[d] —glass adherence ↑ —inactivation of *Candida albicans* →	Mann *et al.*, 1971
?/inhalation/ heavy for 2–5 yr	—morphological changes in surface features —cell yield ↑	Davis *et al.*, 1980
0.3–1.3 mg/kg/ i.p./acute	—% macrophages → —cellular viability →	Gaul and Mellors, 1975
3–30 "joints"/ inhalation/ acute	—inactivation of *S. aureus* ↓ (due to water soluble component of gas phase of fresh smoke) —no. of cells recovered → —differential → —viability →	Pereira *et al.*, 1975
	—cell motility ↓ —cytolysis in hypotonic solution ↑ —release of ß-glucuronidase ↓	Chari-Bitron, 1976
	—inactivation of *S. albus* ↓ (due to water-soluble component of gas phase of fresh smoke)	Huber *et al.*, 1975 McCarthy *et al.*, 1976

TABLE 7 (CONTINUED)

				In Vitro
Species	Sex/Strain	Source	Drug	Concentration (μM)
Rat	♂/CD	broncho-pulmonary lavage	C Smoke	
Rat	♂/CD	broncho-pulmonary lavage	C Smoke	
Rat	♂/CD	lung homogenate	C Smoke, whole/ gas phase	
Rat	♂, ♀/Fischer	whole lung	Δ^9–THC in C Smoke, cannabinoid-free C Smoke	
Mouse	♂/NYLAR–A		Δ^9–THC	
Mouse	♂/Balb/C	peritoneal exudate	Δ^9–THC, CBD	50–100

In Vivo		
Dose/Route/ Duration of Exposure	Observation	Reference
30 "joints"/ day/inhalation/ 30 days	—volume density of lipid inclusions (24 hr postdrug) ↑ —volume density of remaining cytoplasm trend ↓	Davies *et al.*, 1979
30 "joints"/ day/inhalation/ 30 days	—no. of cells recovered → —plastic adherence → —oxygen consumption during phagocytosis ↓ —superoxide formation during phagocytosis ↓ —inactivation of *S. aureus* (24 hr postdrug) →	Drath *et al.*, 1979
15–150 "joints"/ inhalation/ acute	—*in vivo* inactivation of *S. aureus* ↓ (related to water-soluble components of gas phase)	Huber *et al.*, 1979a and b
0.4–5 mg/kg/ inhalation/1 yr	—increased number of macrophage aggregates	Rosenkrantz and Fleischman, 1979
25–200 mg/kg/ p.o./1–7 days	—RES (Kupffer cells) activity →	Munson *et al.*, 1976
	—formation of autophagic vacuoles ↑	Raz and Goldman, 1976

vitro exposure of macrophages to cannabis smoke. A team of investigators from one laboratory has demonstrated a variety of effects after *in vivo* treatment with whole or fractionated cannabis smoke (Huber *et al.*, 1975, 1979a and b; Pereira *et al.*, 1975; McCarthy *et al.*, 1976; Davies *et al.*, 1979; Drath *et al.*, 1979). Acute exposure produced decreased *in vitro* inactivation of *Staphylococcus aureus*. The number of macrophages recovered from the lung, cell viability, and ability to phagocytize bacteria were unchanged (Pereira *et al.*, 1975). The *in vivo* inactivation of *Staphylococcus aureus* was also inhibited (Huber *et al.*, 1979a and b). These effects were apparently related to a water-soluble component of the gas phase of fresh smoke rather than to the cannabinoids. A similar inhibition of inactivation of *Staphylococcus aureus* was observed after *in vitro* exposure of alveolar macrophages to the same smoke fraction (Huber *et al.*, 1975; McCarthy *et al.*, 1976).

Macrophages have also been examined after chronic or subchronic *in vivo* exposure to smoke. After 30 days of exposure, an increase in the volume density of lipid inclusions, accompanied by a decrease in the volume density of the remaining cytoplasm, was observed 24-hr postdrug (Davies *et al.*, 1979). At this time, the number of cells recovered and the phagocytosis and inactivation of *Staphylococcus aureus*, and adherence of the macrophages to plastic were normal, but metabolic changes reflected as decreased oxygen consumption and decreased superoxide formation during phagocytosis were noted (Drath *et al.*, 1979). Rosenkrantz and Fleischman (1979) observed a dose-related focal pneumonitis involving the alveolar macrophages after 87 days of exposure to smoke from marihuana. Similar effects were observed after exposure to cannabinoid-free marihuana smoke, or to tobacco.

From these data, one may conclude that a noncannabinoid component of cannabis smoke is causing irritation of the bronchopulmonary tract and has effects on the macrophage that are reflected by inflammation, structural changes, and disruptions of bacterial inactivation. The cannabinoids may be contributing to changes in cell motility and metabolism.

The phagocytic ability of the reticuloendothelial cells does not appear to be markedly affected by cannabinoids, but the effects of these substances on other types of macrophages are unknown.

The effects of cannabinoids on other cells involved in the immune response have received little experimental attention. There is one observation of decreased ability of polymorphonuclear leukocytes obtained from chronic marihuana smokers to phagocytize yeast cells (Petersen *et al.*, 1975). Clearly, more work is needed in this area.

5. HOST RESISTANCE

If the effects of cannabinoids on specific components of the immune system demonstrated *in vitro* or *in vivo* are of biological significance, it should be possible to demonstrate a deficiency in host resistance to pathogens or foreign cells in cannabis-treated organisms.

Observations in Man

In man, there have been sporadic clinical reports of decreased resistance to a variety of infections. Scholtens (1905) in Surinam described a general decrease of resistance in his chronic cannabis-smoking patients. Many died of tuberculosis or gastroenteritis. Abdulla (1953) reported similar findings in chronic Egyptian users, including an increased prevalence of bilharzia infestations. These observations are difficult to evaluate given the probable adverse living conditions and nutritional status of these users. It is possible, however, that cannabis-induced immunosuppression might be most obvious under such conditions of stress. There is a more recent case report (Juel-Jensen, 1972) of recurrent exacerbations of a genital herpes simplex infection, temporally related to episodes of cannabis smoking in a young male patient. No similar reports have subsequently appeared in the literature.

Cross-sectional comparisons of small numbers of selected heavy cannabis users with nonusing controls matched with respect to age, sex, socioeconomic status, etc., in Jamaica (Rubin and Comitas, 1975), Greece (Boulougouris *et al.*, 1976) or Costa Rica (Coggins *et al.*, 1976), have failed to demonstrate any evidence of increased susceptibility of the users to infectious diseases or neoplasms. Roughly equal numbers of users and controls demonstrated evidence of intestinal parasites (Coggins *et al.*, 1976) and treponemal infections (Rubin and Comitas, 1975). In both these studies, there were no significant differences between the numbers of users and controls with eosinophilia, an immunological response to intestinal parasites that is believed to be T-cell-mediated (Zucker-Franklin, 1974). The subjects in all of these studies numbered less than 100. To date, there have been no large epidemiological studies of the health of cannabis users. This approach would be more likely to reveal mildly impaired resistance to common viral and bacterial infections.

Observations in Animals

In mice treated i.p. with up to 200 mg/kg of various cannabinoids, a dose-related decrease in resistance to both *Listeria monocytogenes* and herpes simplex virus type 2 was demonstrated that paralleled a suppression of T-cell-mediated delayed-type hypersensitivity to sRBC (Morahan *et al.*, 1979). This correlation is significant since resistance to both of these infections is dependent on the function of T-cells and macrophages (Mackaness, 1970; North, 1973; Bloom and Rager-Zisman, 1975). A significant effect was observed at the lowest dose of Δ^9–THC (38 mg/kg), and the threshold dose is therefore unknown. Doses of potent immunosuppressants (5 mg/kg flumethazone in the *L. monocytogenes*-inoculated mice, and 200 mg/kg cyclophosphamide in the herpes-inoculated animals) produced effects that were similar in magnitude to those produced by the highest dose of Δ^9–THC.

There is another possible interpretation for the decreased resistance of cannabinoid-treated animals to bacterial infections that is not directly related to immunosuppression. Bradley *et al.* (1977) in mice and Munson *et al.* (1978) in mice and rabbits observed a lethal interaction of cannabinoids and LPS from several bacteria. These are endotoxins derived from the cell walls of gram-negative bacteria. A similar interaction with LPS is observed with a variety of other drugs, most of which have an inhibitory effect on the synthesis of macromolecules, although the exact mechanism of this phenomenon is unkown. Behavioral observations established that the animals appeared to die from an LPS-induced enhancement of cannabinoid-induced effects (rather than vice versa) suggesting that LPS is shifting the dose-response curve of the cannabinoids to the left, possibly by increasing the permeability of the blood-brain barrier (Munson *et al.*, 1978). Although this effect occurred in rabbits at doses of Δ^9–THC relevant to those smoked by heavy human cannabis users, a similar potentiation of marihuana-induced behavioral effects has not been reported in humans infected with gram-negative bacteria.

6. TOLERANCE

The question of tolerance is relevant to the area of cannabis-induced effects on immune function for two reasons. Firstly, if tolerance develops to cannabinoid-induced manifestations of immunosuppression, one would expect that these effects would tend to diminish over a period of chronic exposure provided that the dose was kept constant. On the other hand, the therapeutic usefulness of these drugs if used as immunosuppressants would also diminish. Secondly, the production of antibodies specific to Δ^9–THC has been proposed as a mechanism for the development of tolerance to other effects of the drug.

Development of Tolerance to Effects on the Immune System

It is not well established in animals that tolerance can develop to cannabinoid-induced immunosuppression, although since this phenomenon appears to be almost universal with other effects of the drug (Jones, this volume) its demonstration would not be surprising. There is some evidence (see Section 3) that effects on lymphoid organs are less apparent after long-term treatment. There are few experimental studies pertinent to the development of tolerance to effects on cellular immunity or macrophage function, since most investigators treated their subjects with cannabinoids acutely or for short periods, and serial determinations of effects after various periods of drug administration were not made. Daul and Heath (1975) observed that effects on both cellular and humoral components were more pronounced after six months than after three months.

There are two studies in rodents that are relevant to the development of tolerance to cannabinoid-induced suppression of humoral immunity. Loveless and Munson (1976) observed that mice pretreated for five days with a daily dose of 5 or 10 mg/kg Δ^8–THC demonstrated a smaller decrease in splenic PFC when challenged with an acute dose of 60 mg/kg Δ^8–THC given two days after immunization with sRBC than nonpretreated mice. On the other hand, Luthra *et al.* (1980) reported a lack of tolerance development to Δ^9–THC-induced splenic atrophy, reduced PFC response, and reduced HT and HS titers despite up to 21 days of treatment with 10 mg/kg of the drug before immunization. These observations are difficult to reconcile, but may have been due to differences in experimental design (i.e., cannabinoid, species, dose, etc.).

Antibody Formation as a Mechanism of Tolerance Development

Nahas *et al.* (1973b) observed that the development of tolerance to the hypotensive effects of Δ^9–THC was attenuated in spontaneously hypertensive rats treated with immunosuppressants. Other investigators have actively or passively immunized animals with THC-protein conjugates and have observed reduced behavioral effects on subsequent challenge with Δ^9–THC (see Section 4). These groups have postulated that antibodies directed against cannabinoids could effectively remove the drugs from circulation, thus decreasing the intensity of their effects.

It is unlikely, however, that this mechanism is a major factor in the development of tolerance. Tolerance can begin to develop to the behavioral effects of cannabis in both humans and animals within two to five days (see Jones, this volume), i.e., much faster than an antibody response could be mounted that would be sufficient to attenuate the effects of Δ^9–THC. Generally, at least 5–7 days would be required for this process. Of course this does not rule out the possibility that this process might be acting in parallel with other dispositional and functional mechanisms in the final expression of tolerance.

7. POSSIBLE MECHANISMS OF ACTION

In an attempt to understand the mechanisms that underly the ability of cannabinoids to disrupt the competency of lymphoid cells, we have reviewed the available data pertaining to the direct effects of these substances on lymphoid and nonlymphoid tissues, cells, and subcellular components. Another line of evidence that suggests that cannabinoids may cause immunosuppression indirectly by inducing steroid release will also be discussed.

Direct Effects on Cellular Function

A number of investigators have observed the *in vitro* effects of a variety of cannabinoids on cultures of lymphocytes, normal mammalian tissues, mammalian neoplastic cells, and nonmammalian cells. Generally studied in these experiments were effects on cell growth and division, respiration, organelles such as lysosomes, membranes, and the synthesis of macromolecules. The actions of cannabinoids on these parameters are summarized in Tables 6 and 8 and will be discussed below.

Effects on Cell Growth

Cannabinoid-induced inhibition of cell growth and division has been observed in virtually every cell type studied. The slime mold *Dictyostelium discoideum* was affected (Bram and Brachet, 1976), as were the protozoa *Naegleria fowleri* (Pringle *et al.*, 1979) and *Tetrahymena pyriformis* (McClean and Zimmerman, 1976), murine Lewis lung carcinoma cells (White *et al.*, 1976) and neuroblastoma cells (Huot, 1976; End *et al.*, 1977), rat glioma cells (End *et al.*, 1977), African green monkey fibroblastic cells (Huot, 1976), human epidermoid neoplastic cells (Huot, 1976) and cervical carcinoma cells (Blevins and Smith, 1980). Replication of herpes simplex virus types 1 and 2 in human cell cultures was also inhibited *in vitro* by Δ^9–THC, but it is unknown whether the drug was affecting the virus directly, or altering the properties of the host cells (Blevins and Dumic, 1980). The effects were dose-related, and were generally observed at *in vitro* cannabinoid concentrations between 1 and 100 μM. It appears that the molecule can be substantially altered without loss of activity. Pringle *et al.* (1979), in a study involving 17 different cannabinoids, found that only the hydroxyl group on the phenolic ring was required for antinaeglerial action.

The administration of cannabinoids (25–200 mg/kg p.o.) for 10 days to mice inoculated with Lewis lung carcinoma cells also produced *in vivo* inhibition of tumor growth (Munson *et al.*, 1975; Carchman *et al.*, 1976), thus tending to confirm the *in vitro* results with neoplastic cells. The *in vivo* growth of L1210 lymphoma cells was unaffected, however, suggesting that cannabinoids may be more effective against cells with longer doubling times (Munson *et al.*, 1975). Δ^9-THC, Δ^8-THC, CBN, and abnormal Δ^8-THC were active, while abnormal CBD was ineffective and CBD even appeared to stimulate tumor growth (Munson *et al.*, 1975; Carchman *et al.*, 1976).

Effects on Synthesis of Macromolecules

There is general agreement that *in vitro* exposure to cannabinoids inhibits the intracellular synthesis of macromolecules. Inhibition of the incorporation of radiolabeled precursors of nucleic acids and proteins has been observed in almost every system studied including mitogen-stimulated human and animal lymphocytes (see Section 4), rat brain slices (Jakubovič and McGeer, 1972), rat testicular slices and cell suspensions (Jakubovič and McGeer, 1977), rat Leydig cells (Jakubovič *et al.*, 1979a and b), rat spermatogonial cells (Jakubovič *et al.*, 1979a), mouse bone marrow (Carchman *et al.*, 1976), the protozoa *Tetrahymena pyriformis* (McClean and Zimmerman, 1976), and *Naegleria fowleri* (Pringle and Bradley, 1978) and a variety of human and animal neoplastic cells (see Table 8). Although there is some variation among cell types, the required concentration of cannabinoids to produce 50% inhibition is in the order of 10–100 μM. Part of the variability in sensitivity can be accounted for by differences in the rate of cellular uptake of cannabinoid which, in turn, is related to the extent of drug binding in the different culture media (End *et al.*, 1977).

Most investigators have found that the synthesis of nucleic acids and particularly that of DNA was the most sensitive to the action of cannabinoids (Blevins and Regan, 1976; End *et al.*, 1977; Blevins and Smith, 1980). Blevins and Regan (1976) reported that semiconservative DNA synthesis is more affected than DNA repair. In one study, RNA synthesis appeared to be more sensitive than DNA synthesis (McClean and Zimmerman, 1976). Protein synthesis appears to be the least affected (End *et al.*, 1977; Jering and Toro-Goyco, 1979). Other investigators, however, have reported that the syntheses of DNA, RNA, and protein were equally sensitive to cannabinoid-induced inhibition (Pringle and Bradley, 1978). A similar pattern of inhibition of DNA synthesis was observed *in vivo* in Lewis lung tumor tissue grown in mice treated i.p. with 200 mg/kg of various cannabinoids (Friedman, 1977). Protein synthesis was not affected by similar doses.

There is still considerable controversy regarding the mechanism of cannabinoid-induced inhibition of DNA, RNA, and protein synthesis. It

TABLE 8

Actions on Tissues, Cells, and Subcellular Components

			In Vitro	*In Vivo*	
Preparation	Source	Drug	Concentration (μM)	Dose (mg/kg)/ Route/ Duration of Exposure (Days)	Growth Rate
Brain slices	rat	Δ^9-THC, CBD, CBG	10–100		
Ileum	rat	Δ^9-THC	6		
Erythrocytes, liver mitochondria	rat	Δ^9-THC	2–100		
Testicular slices, cell suspensions	rat	Δ^9-THC, Δ^8-THC, 11-OH-Δ^9-THC, 8-ß-OH-Δ^9-THC, CBD, CBN, CBG, SP-111A	10–100		

a) decrease b) no change c) increase d) variable change

Observations				
Macromolecular Synthesis	Effects on Precursor Pool	Respiration (O_2 Consumption)	Membrane Effects	Reference
protein ↓[a]		→		Jakubovič and McGeer, 1972
RNA ↓				
			Na$^+$-K$^+$-ATPase activity ↓	Laurent and Roy, 1975
			Mg^{++}-ATPase activity ↓	
			Na$^+$-K$^+$-ATPase activity ↓	Chari-Bitron, 1976
			Mg^{++}-ATPase activity ↓	
protein ↓ RNA ↓	precursor pool ↓	→		Jakubovič and McGeer, 1977
DNA ↓				

TABLE 8 (CONTINUED)

			In Vitro	*In Vivo*	
Preparation	Source	Drug	Concentration (μM)	Dose (mg/kg)/ Route/ Duration of Exposure (Days)	Growth Rate
Leydig cells	rat	Δ^9–THC, Δ^8–THC, 11-OH-Δ^9–THC, 8–ß–OH–Δ^9–THC, CBD, CBN, CBG, SP–111A	15–150		
Spermatagonial cells	rat	Δ^9–THC, Δ^8–THC, 11-OH-Δ^9–THC, 8–ß–OH–Δ^9–THC, CBD, CBN, CBG, SP–111A	5–100		
Bone marrow	mouse	Δ^9–THC, Δ^8–THC, abnor. Δ^8–THC, CBN	0.1–10		
Brain synaptosomes	mouse	Δ^9–THC, CBD	5–50		
Brain mitochondria microsomes	mouse	Δ^9–THC	1–40		

Observations				
Macromolecular Synthesis	Effects on Precursor Pool	Respiration (O_2 Consumption)	Membrane Effects	Reference
protein ↓				Jakubovič *et al.* 1979a and b
protein ↓ RNA ↓		→		Jakubovič *et al.*, 1979a
protein ↓				Carchman *et al.*, 1976
			Na^+–K^+–ATPase activity ↓ Mg^{++}–ATPase activity ↓	Hershkowitz *et al.*, 1977
			Na^+–K^+–ATPase activity ↓ Mg^{++}–Ca^{++}–ATPase activity ↓ Mg^{++}–ATPase activity ↑↓[d]	Bloom *et al.*, 1978

TABLE 8 (CONTINUED)

			In Vitro	In Vivo	
Preparation	Source	Drug	Concentration (μM)	Dose (mg/kg)/ Route/ Duration of Exposure (Days)	Growth Rate
Brain synaptosomes	mouse	Δ^9–THC	0.1–1		
Lewis lung carcinoma cells	mouse	Δ^9–THC, Δ^8–THC, abnor. Δ^8–THC, CBN	0.1–10		
L1210 lymphoma cells					
Lewis lung carcinoma cells	mouse	Δ^9–THC	10–100		
Lewis lung carcinoma cells	mouse	Δ^9–THC, Δ^8–THC, CBD, abnor. CBD		200/i.p./ acute	
Lewis lung carcinoma cells	mouse	Δ^9–THC, Δ^8–THC, abnor. Δ^8–THC, CBN, CBD, abnor. CBD		25–200/ p.o./10	↓
Lewis lung carcinoma cells	mouse	Δ^9–THC, Δ^8–THC, CBN		25–200/ p.o./10	↓
		CBD		25–200/ p.o./10	↑[c]

Observations				
Macromolecular Synthesis	Effects on Precursor Pool	Respiration (O_2 Consumption)	Membrane Effects	Reference
			lysophosphatidyl-choline acyltransferase activity ↓	Greenberg *et al.*, 1978
DNA ↓				Carchman *et al.*, 1976
DNA ↓	precursor pool →			White *et al.*, 1976
DNA-reversible ↓ protein →				Friedman, 1977
				Carchman *et al.*, 1976
				Munson *et al.*, 1975

TABLE 8 (CONTINUED)

			In Vitro	*In Vivo*	
Preparation	Source	Drug	Concentration (μM)	Dose (mg/kg)/ Route/ Duration of Exposure (Days)	Growth Rate
L1210 lymphoma cells	mouse	Δ^9–THC, Δ^8–THC, CBN, CBD		25–200/ p.o./10	→
L1210 lymphoma cells	mouse	Δ^9–THC	1–100		
diploid fibroblasts	human	Δ^9–THC	3.2–32		
neuroblastoma cells	human				
neuroblastoma cells	mouse				
HeLa cervical carcinoma cells	human	Δ^9–THC	3.2–100		cell division ↓
KB epidermoid neoplastic	human	Δ^9–THC	0.1–10,000		proliferation ↓
AGM fibroblastic cells	African green monkey				

Observations				
Macromolecular Synthesis	Effects on Precursor Pool	Respiration (O_2 Consumption)	Membrane Effects	Reference
	uptake of precursors ↓			Desoize *et al.*, 1979a and b
protein ↓ RNA ↓ DNA (semi-conservative ↓) DNA (repair) →	precursor pool ↓ transport of precursors →			Blevins and Regan, 1976
	nucleotide pool ↓↑			Blevins and Smith, 1980
DNA template activity ↓			Na^{+}–K^{+}–ATPase activity, biphasic effect	Huot, 1976

TABLE 8 (CONTINUED)

			In Vitro	*In Vivo*	
Preparation	Source	Drug	Concentration (μM)	Dose (mg/kg)/ Route/ Duration of Exposure (Days)	Growth Rate
NS–20 neuroblastoma cells	mouse				
NB2A neuroblastoma cells	mouse	Δ^9–THC	1–100		growth ↓
C–6 glioma cells	rat				
Ehrlich ascites cells	mouse	Δ^9–THC	5–200		
Reuber H–35 hepatoma cells		Δ^9–THC	20–150		
HTC cells	rat	Δ^9–THC	150		
Y–1 cells	mouse	Δ^8–THC			
C–6 glioma cells	rat				
NB2A neuroblastoma cells	mouse	Δ^9–THC, Δ^8–THC	150		

Observations				
Macromolecular Synthesis	Effects on Precursor Pool	Respiration (O_2 Consumption)	Membrane Effects	Reference
protein ↓ RNA ↓ DNA ↓	uptake of precursors ↓			End *et al.*, 1977
DNA ↓		→	Na^+-K^+-ATPase activity ↓	Toro-Goyco *et al.*, 1978
protein → RNA → DNA ↓	DNA precursor pool ↓			Jering and Toro-Goyco, 1979
protein ↓ RNA ↓ DNA ↓				Carchman *et al.*, 1979
protein → RNA ↓ DNA ↓				

TABLE 8 (CONTINUED)

			In Vitro	*In Vivo*	
Preparation	Source	Drug	Concentration (μM)	Dose (mg/kg)/ Route/ Duration of Exposure (Days)	Growth Rate
HeLa cervical carcinoma cells	human	Δ^9–THC, Δ^8–THC, 11–OH–Δ^9–THC, CBN	1–40		
Dictyostelium discoideum		Δ^9–THC, CBN	10–125		proliferation ↓ differentiation ↓
Tetrahymena pyriformis		Δ^9–THC	3.2–24		growth rate ↓ cell division ↓
Naegleria fowleri		Δ^9–THC and analogs	30		
Naegleria fowleri		Δ^9–THC and analogs	15–150		↓
Lewis lung carcinoma cells	mouse	Δ^9–THC	10–100		

Observations				
Macromolecular Synthesis	Effects on Precursor Pool	Respiration (O_2 Consumption)	Membrane Effects	Reference
protein ↓ RNA ↓ DNA ↓	precursor pool ↓			Stein *et al.*, 1979
				Bram and Brachet, 1976
protein ↓ RNA ↓ DNA ↓	precursor pool ↓			McClean and Zimmerman, 1976
protein ↓ RNA ↓ DNA ↓				Pringle and Bradley, 1978
				Pringle *et al.*, 1979
DNA ↓	precursor pool →[b]			Munson *et al.*, 1975

is agreed that cannabinoids at concentrations below 100 μM do not act by causing cell death. Cell viability has repeatedly been confirmed by testing for the exclusion of the dye trypan blue (see, for example, Blevins and Smith, 1980). There are several other possible explanations for this phenomenon, however, and published evidence to support almost every one of them. These are discussed below.

The synthesis of macromolecules is dependent on the intracellular availability of precursors and the function of sets of specific enzymes. Most authors have reported that *in vitro* exposure to concentrations of cannabinoids sufficient to inhibit macromolecular synthesis produced a reduction in the size of the radiolabeled acid-soluble precursor pools (Blevins and Regan, 1976; McClean and Zimmerman, 1976; White *et al.*, 1976; Jakubovic and McGeer, 1977; Desoize *et al.*, 1979a and b; Jering and Toro-Goyco, 1979; Stein *et al.*, 1979). One group of investigators using Lewis lung tumor cells found no change in the size of the precursor pool (Munson *et al.*, 1975; White *et al.*, 1976). The reason for this discrepancy is not clear, but may be related to a factor peculiar to this line of cells.

Several investigators explained the decreased pool size by demonstrating a decrease in uptake of radiolabeled precursors such as thymidine, uridine, and leucine into the cells (End *et al.*, 1977; Desoize *et al.*, 1979a and b). Stein *et al.*, (1979) demonstrated that a cannabinoid-induced inhibition of precursor uptake was not secondary to an increase in the size of the intracellular pool of nonlabeled precursors. Since transcription in isolated chromatin and nuclei was unchanged by exposure to cannabinoids, these authors concluded that nucleic acid synthesis was impaired as a result of decreased transport of precursors at the level of the cell membrane. Blevins and Regan (1976) did not observe a decrease in precursor uptake, and suggested that cannabinoids might decrease pool size by increasing the permeability of cell membranes. Desoize *et al.* (1979a and b), however, reported the Δ^9-THC does not affect cellular "leakage" as demonstrated by the kinetics of a labeled amino acid, aminoisobutyric acid. These investigators also demonstrated that Δ^9-THC did not affect the binding of a DNA precursor, thymidine, to its membrane carrier protein and concluded that the substance may be producing a nonspecific alteration of the membrane configuration which could inhibit the function of membrane-bound transport systems.

Jakubovič and McGeer (1977) observed a cannabinoid-induced inhibition of phosphorylation of nucleic acid precursors, and suggested that these substances may be acting by reducing the availability of ATP. Pringle and Bradley (1978) also concluded that since in their study DNA, RNA, and protein synthesis were inhibited at similar concentrations of cannabinoids and over a similar time course, the inhibition was secondary to a primary decrease in generation of a common precursor such as ATP.

Virtually all cannabinoids tested were active in inhibiting the synthesis of macromolecules (Carchman *et al.*, 1976; Jakubovič and McGeer, 1977; Pringle and Bradley, 1978; Stein *et al.*, 1979), although potency was lost by removing the hydroxyl group of the phenolic ring (Pringle and Bradley, 1978), opening the pyran ring (e.g., CBD), or hydroxylating or otherwise altering the cyclohexane ring (e.g., 8β, 11-OH-Δ^9-THC, CBCh, CBC) (Carchman *et al.*, 1976).

Effects on Respiration

Four *in vitro* studies performed on a variety of cells (Table 8) indicate that cannabinoids do not significantly inhibit cellular respiration as measured by 0_2 consumption at concentrations that are sufficient to inhibit the synthesis of macromolecules (Jakubovič and McGeer, 1972, 1977; Jakubovič *et al.*, 1979a; Toro-Goyco *et al.*, 1978). It is therefore unlikely that cannabinoids are affecting cell function by inhibiting respiration.

Effects on Lysosomes

Δ^9-THC was found to lyse rat liver lysosomes *in vitro* at concentrations greater than 100 μM (Mellors, 1976). Subfractionation of liver homogenates from rats treated i.v. with ^{14}C-Δ^9-THC revealed that radioactivity accumulated in the soluble enzyme fraction of the lysosomes, but not in the lysosomal membrane fractions or in the other organelles. The *in vitro* fragility of lysosomes of rats treated for 30 days with 4-30 mg/kg Δ^9-THC was also increased. These findings could possibly be related to observed changes in macrophage function reported in Section 4.

Effects on Cell Membranes

Cannabinoids appear to be influencing the function of the cell membrane as reflected by changes in the activities of several membrane-bound enzymes (Tables 6 and 8). Increases in membrane ATPase activity and phospholipid synthesis are biochemical markers of blastogenesis (Mellors, 1976). Studies of the effects of cannabinoids on these functions in lymphocytes and other cells have been performed in an attempt to elucidate the mechanism(s) of action of these compounds.

Δ^9-THC, in a dose-related manner at concentrations less than 100 μM, appears to inhibit the activity of $(Na^+ + K^+)$-ATPase, Mg^{++}-ATPase and $(Mg^{++} + Ca^{++})$-ATPase obtained from a variety of sources (Laurent and Roy, 1975; Chari-Bitron, 1976; Hershkowitz *et al.*, 1977;

Bloom *et al.*, 1978; Toro-Goyco *et al.*, 1978). The latter group simultaneously demonstrated an inhibition of protein synthesis in Ehrlich ascites cells. Huot (1976) observed a slight stimulation of $(Na^+ + K^+)$–ATPase from African green monkey fibroblastic cells at a similar concentration, but an inhibition at higher ones. The reason for this difference in sensitivity is not clear. Toro-Goyco *et al.* (1978) have suggested that Δ^9–THC, by inhibiting membrane ATPases, may be interfering with the active transport of amino acids, nucleosides, and other essential nutrients into the cell, and with the phosphorylation of nucleosides. These actions could account for the decreased rate of synthesis of macromolecules discussed previously in this section.

Other membrane-bound enzymes that have been reported to be inhibited by Δ^9–THC are lysophosphatidyl-choline acyltransferase in mouse brain synaptosomes (Greenberg *et al.*, 1978) and in Con A-stimulated splenic lymphocytes (Greenberg and Mellors, 1978) and lysolecithin acyltransferase in Con A-stimulated mouse splenic lymphocytes (Greenberg *et al.*, 1977). Acyltransferase activity is inhibited *in vitro* at far lower concentrations of Δ^9–THC (<1.0 μM) than are other cell functions. A comparison with other lipid-soluble drugs suggested that the effect is greater than would be expected simply on the basis of its solubility in biological membranes (Greenberg *et al.*, 1978). These authors therefore concluded that the inhibition is "due to a process that is more specific than the perturbation of the surrounding lipid bilayer" that was demonstrated at higher concentrations in lecithin-cholesterol liposomes by Gill and Lawrence (1976). Acyltransferases are known to be closely associated with activation of the cell-mediated immune response (Fisher and Mueller, 1968; Ferber and Resch, 1973) and are important in the maintenance and alteration of membrane structure. Nonpsychoactive cannabinoids inhibit the same enzymes, but at much higher concentrations (100–1000 μM) when they are probably influencing membrane fluidity and volume in a nonspecific manner (Greenberg and Mellors, 1978). These cannabinoid concentrations, however, are still reasonably close to those required *in vitro* to inhibit cellular growth and the synthesis of macromolecules.

It is still impossible to specify the exact mechanism by which the cannabinoids act. Cellular events are interrelated so closely that perturbation of one function may alter many other components in such a way that it is extremely difficult to determine whether an observed change is related to a primary site of action or is secondary to another effect. The stereospecificity and dose requirements of many of the above effects differ, which suggests that there may be more than one mechanism of action. It is tempting to try to explain all of the *in vitro* effects by means of a membrane model. However, the participation of membrane effects in other cell functions is not yet clear and it would be premature to make this conclusion at the present time.

Indirect Effects on Immune Function

It has also been postulated that cannabinoid-induced release of corticosteroids may mediate at least some of the effects on lymphoid elements. Cannabinoids can stimulate the release of corticosteroids by means of an effect on the pituitary adrenal axis at doses that are comparable to those producing immunosuppression (Cicero, 1980; Bloch, this volume). Glucocorticosteroids are also known to affect virtually every function of the immune system, as well as inflammatory reactivity (Fauci, 1979).

By using adrenalectomized mice maintained on low doses of corticosterone, Smith (1979) was able to eliminate cannabis-induced corticosteroid release. She found that a decrease in spleen weight associated with a loss of cellularity appeared shortly after treatment with Δ^9–THC in control and sham-operated mice, but not in adrenalectomized mice. The Δ^9–THC-induced reduction in peripheral leukocyte counts was also delayed in the adrenalectomized animals. These results suggested that corticosteroid release contributes to the decrease in splenic cellularity and the initial decrease in peripheral leukocytes. Otherwise, however, the primary antibody response to sRBC in adrenalectomized mice appeared intact. This suggests that cannabinoids can have a direct effect on lymphoid tissues independently of the adrenal gland.

Smith (1979) also postulated that cannabinoids themselves may be exerting steroid-like effects. In other endocrine systems, this is thought to be the case, although the ability of Δ^9–THC to interact with steroid receptors is controversial (Bloch, this volume). For example, in rat HTC cells, a steroid sensitive line, the combination of Δ^8–THC and the synthetic steroid, dexamethasone, inhibited the synthesis of nucleic acids and proteins more effectively than would be expected from a summation of their individual effects (Carchman *et al.*, 1979). The cannabinoid appeared to act by increasing the uptake of the steroid and facilitating the translocation of the steroid/receptor complex to the nucleus, but did not affect the steroid-receptor binding. The *in vitro* studies of the interaction of corticosteroids and cannabinoids on lymphoid cell function that are needed to evaluate this hypothesis have not yet been performed.

8. SUMMARY AND CONCLUSIONS

At present, there is no conclusive evidence that consumption of cannabinoids predisposes man to immune dysfunction as measured by the following immunological indicators: the number of T-lymphocytes, B-lymphocytes, or macrophages; the function of T-lymphocytes, B-lymphocytes, or macrophages; and serum immunoglobulin levels. There is suggestive evidence that T-lymphocytes may be impaired as reflected by an impaired reaction to allogeneic lymphocytes, reduced responsiveness to the T-cell mitogen, PHA, and reduction in the number able to form early rosettes with sRBC. The phagocytic ability of polymorphonuclear leukocytes may also be impaired in marihuana smokers.

Most likely all of the cannabinoids can act as haptens; thus the potential for allergic reactions is present. Antibodies against Δ^9-THC have been made.

There is consistent evidence that cannabinoids administered parenterally or by inhalation induce defects in both the cell-mediated and humoral immune systems of rodents and that rats are more sensitive than mice to these effects. Humoral immune suppression, as measured by decreased antibody-forming responses to T-dependent and T-independent antigens and a decreased lymphocyte response to a B-cell mitogen, has been observed. The degree of immunosuppression is a function of the temporal relationship between the administration of the cannabinoid and the antigen. The effects are more pronounced if the cannabinoids are administered during the early phase of antibody formation. Cell-mediated immune suppression, as measured by a reduction of the delayed-type hypersensitivity response to several antigens and a decreased lymphocyte response to PHA, also occurs. Resistance to *L. monocytogenes* and herpes simplex virus is decreased. The degree to which tolerance develops to these effects is unclear.

The doses required to produce ~~these~~ such immunosuppressant effects in animals have been variable. While some investigators have reported suppression of at least some of the components of the immune response at behaviorally relevant doses of Δ^9-THC (<25 mg/kg in the mouse, <10 mg/kg in the rat and <2 mg/kg in the monkey), others have required doses high enough to cause profound sedation in order to produce a significant effect. This inconsistency may reflect differences in the sensitivity of the various assays used. In addition, some components of the immunological system ~~(e.g., the cell-mediated DTH response~~) may be more sensitive to the effects of the drug than others.

The evidence for a cannabis-induced inhibition of monocyte/macrophage function is mixed. Overall, there appears to be a transient reduction in the ability of smoke-exposed rat bronchopulmonary lavage cells to kill staphylococci, along with decreased lysosomal enzyme release, superoxide formation, and oxygen consumption. These effects appear to be related to noncannabinoid components of the smoke.

The mechanisms by which cannabinoids produce immunosuppression in animals are not clear. Certain effects (e.g., splenic atrophy) may be mediated indirectly by a drug-induced steroid release, while others (e.g., inhibition of antibody formation) seem to be the result of direct effects on the lymphoid cells. The subcellular site of action of these effects appears to be related to a cannabinoid-induced inhibition of DNA, RNA, and/or protein synthesis although the primary site of action is still unknown. In *in vitro* studies, inhibition occurs at cannabinoid concentrations between 1 and 100 μM and may be secondary to decreased uptake of nucleosides or amino acids, decreased availability of ATP, or inhibition of enzymes necessary for the synthesis of macromolecules.

In the extrapolation of the *in vitro* results to the whole organism and then to man, it is important to relate the concentrations used to the levels observed in cannabinoid-exposed animals and humans. Using some gross approximations, a rough calculation can be made.

Assuming that the cannabinoids were distributed evenly in body tissues (which is not the case), a mouse with a density of 1.1 g/ml and receiving 25 mg/kg Δ^9–THC would have a drug concentration of 22.7 μg/ml or about 72 μM. Similarly, the concentration in a rat receiving 10 mg/kg would be about 29 μM. Cannabinoids produce at least some of these effects at similar concentrations *in vitro*. Granted, there have been no allowances made for reductions in the actual concentrations due to tissue sequestration, protein binding, or biotransformation *in vivo*. *In vitro*, however, cannabinoids adhere to glass and bind to the proteins of the culture media. This also reduces their effective concentrations. The *in vivo* significance of biotransformation is unknown since at least some of the metabolites are known to be active *in vitro*. On the basis of such very rough approximations, it might be concluded conservatively that the results of *in vitro* studies may give insight into the cellular and subcellular effects of the cannabinoids.

It is likely that the degree of immunosuppression produced by different doses of cannabis, like that of other immunosuppressants, will vary along a continuum, ranging from slight effects on resistance to infections, to a marked decrease in resistance resulting in death of the host. It is likely that we would now be aware of profound changes in the resistance of human cannabis smokers if these occurred frequently. However, we lack the epidemiological observations on large numbers of users that would be necessary to establish the occurrence of small degrees of impairment that are suggested by the animal experiments, and which would likely be reflected by a slight increase in the incidence, severity, and duration of common infections. This type of effect could ultimately be a significant public health issue. This is particularly true in the case of users who are already immunosuppressed such as transplant patients, cancer patients, and those with immune disorders.

Recommendations for Further Research

Of the total of 106 cannabis-related reports on immune function selected for review, only two were published in 1981. It is unfortunate that interest in and support for this work are declining at a time when many new and more sensitive techniques have become available in this rapidly developing field. Based on the evidence reviewed, we offer several research recommendations in areas where we feel further work would be fruitful.

Ideally, studies in man should include the following immunological workup: clinical history and evaluation; immunoglobulin levels; primary and secondary antibody responses; number of monocytes and their phagocytic ability; numbers of T- and B-lymphocytes including the subpopulations of T-lymphocytes; cell-mediated immune response to recall antigens; lymphocyte response to mitogens and MLC; polyclonal activation of B-lymphocytes; and analyses of serum complement. It should be noted that this type of workup may not demonstrate a cannabis-induced perturbation conclusively. The normal range in these parameters is very large and a small but important effect may not be demonstrable in small numbers of users. Therefore, less comprehensive but larger scale epidemiological studies of the health status of cannabis users are also recommended, since subtle defects in resistance to common infections or cancer are more likely to be detected in very large populations.

Studies in animals should take two directions; the first is the use of the time-tested toxicological protocols and the second, a mechanistic approach. For the toxicological studies, at least two species and both sexes should be used. Acute, subchronic 14- and 90-day studies should be performed, in which the marihuana and/or cannabinoids are administered by the appropriate routes. An examination of the humoral immune system should include measurements of IgM and IgG spleen antibody-forming cell response to a T-dependent antigen; IgM spleen antibody-forming cell response to a T-independent antigen; serum immunoglobulin levels of IgM, IgG and IgD, and spleen and blood lymphocyte response to the B-cell mitogen, bacterial LPS.

A study of cell-mediated immunity should encompass assays of the delayed-type hypersensitivity response to a T-cell antigen; and spleen and blood lymphocyte responses to the T-cell mitogens, PHA and/or Con A, and to allogeneic lymphocytes.

Investigations of monocyte/macrophage function should include vascular clearance and phagocytosis of a test particle by the organs of the reticuloendothelial system; where possible, enumeration of peritoneal, alveolar, and/or pleural cells from lavages; a determination of the number of plastic or glass adherent cells obtained from the lavages; and the phagocytic, bactericidal, and tumoricidal or tumoristatic activities of the adherent cells.

The routine parameters performed in a classical toxicological study which include hematology, clinical chemistry, organ weights and histopathology, food and water consumption, and growth rate should also be assessed. Bone marrow cells should be studied with regard to number per femur, the rate of DNA synthesis, and the number of stem cells. From all of the above data, a risk assessment for man could then be made.

For the mechanistic studies, the following questions should be addressed: What is the role of the adrenal in the immunosuppressant activity? Which immune cell type is most affected? What is the biochemical site of action? Does tolerance develop to the immunosuppressant effects of cannabis and, if so, what is the mechanism? Is there an interrelationship between nutritional status and cannabis-induced immunosuppression?

The possibility of an enhanced immunosuppression due to the interaction of cannabis with other drugs is a problem that is relevant to both street drug users and cancer patients undergoing immunosuppressive chemotherapy. This question should be given further attention.

Studies of the nature outlined here should help to determine whether cannabinoid-induced immunosuppression is likely to be a significant clinical problem.

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Effects of Marihuana and Cannabinoids on Reproduction, Endocrine Function, Development, and Chromosomes

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1. INTRODUCTION

The widespread consumption of marihuana in the North American population and in others, especially among young adults, raises concern about the possible effects of this psychoactive plant product on endocrine, reproductive, developmental, and genetic processes. The past fifteen years have seen an increasing, but topically uneven, number of studies devoted to assessing the influence of marihuana and cannabinoids on these processes. This paper consists of a selective review and evaluation of the progress made in documenting and delineating marihuana activity in these areas and in determining loci and mechanisms of action. It is also intended to indicate where our knowledge and understanding are incomplete, absent, or incorrect.

2. THE REPRODUCTIVE SYSTEM IN ANIMALS

Marihuana, crude marihuana extracts (CME), Δ^9-tetrahydrocannabinol (Δ^9-THC), and certain other purified cannabinoids can be shown to depress the functioning of the male reproductive endocrine system. The loci of action are at both the hypothalamic-brain and the testicular levels. Both chronic and acute effects are observed, with most effects being reversible. In the female, acute cannabinoid administration can rapidly depress gonadotrophin release and delay or block ovulation; although a site of action exists at the higher neural centers, Δ^9-THC also exerts direct effects on the uterus. In addition, a less well defined long-term interference with reproductive activity is seen. Actions specific to the pregnant female have not been delineated. A wide range of doses and

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routes of administration has been used to elicit effects. Few dose-response relationships have been established *in vivo*. The primary species studied is the rat, although some work in the mouse and Rhesus monkey has been reported.

Male Reproductive System

Testicular Androgenic Activity

Testicular endocrine activity diminishes during chronic CME or Δ^9-THC exposure. Prostate, seminal vesicle, and epididymal weights are decreased, and there is involution of the prostatic and seminal vesicle secretory epithelium (Table 1) (reviewed in Bloch *et al.*, 1978). Seminal vesicle fluid volume and fructose content are also reduced; e.g., chronic treatment p.o. with 75 mg CME or 25 mg Δ^9-THC/kg in the rat lower both by about 50% (Fujimoto *et al.*, 1978, 1979). So are testicular prostatic and epididymal ascorbic acid levels (Chakravarty, 1980). Seminal vesicle ascorbic acid levels are affected marginally. In one report, mouse levator ani mass diminished (Dixit *et al.*, 1974). These effects are reversible; organ weights returned to pretreatment status one to two months after the cessation of treatment lasting six weeks to six months (Dixit *et al.*, 1974; Rosenkrantz *et al.*, 1975; Fujimoto *et al.*, 1978, 1979).

The regression of the prostate and seminal vesicles presumably reflects diminished androgenic stimulation, although a direct effect of cannabinoids cannot be excluded. Collu *et al.* (1975) and Collu (1976) noted reduced prostate weights in prepuberal rats given 10 mg Δ^9-THC/kg. The same doses of Δ^9-THC and CBN largely prevented replacement doses of testosterone or dihydrotestosterone from maintaining prostate or seminal vesicle weights in castrated adult rats (Purohit *et al.*, 1979). Similarly, Δ^9-THC counteracted the maintenance effect of human chorionic gonadotrophin (hCG) given to hypophysectomized rats but did not influence plasma testosterone values. Purohit's group (1980) recently reported an *in vitro* inhibitory effect of a 100–1,000-fold excess of a variety of cannabinoids on dihydrotestosterone binding by rat prostate cytosol. Δ^9-THC, CBN, and the metabolites, 11-OH-Δ^9-THC and 8β-OH-Δ^9-THC were the most potent, with K_i values in the range of 0.2–0.3 μM. In contrast, ^{3}H-testosterone uptake by ventral and anterior prostate, seminal vesicles and testes *in vivo* was not affected by prior i.p. injection of 4 or 16 mg Δ^9-THC/kg/day into adult rats for four days (Ling *et al.*, 1973).

Acute cannabinoid administration depresses plasma testosterone levels (Table 2). Reductions of 60%–75% were seen 2 to 4 hr after 5 mg Δ^9-THC/kg was given i.p. to rats (Symons *et al.*, 1976), or 50 mg/kg was given orally to mice (Dalterio *et al.*, 1978). Chronic administration of Δ^9-THC (5–10 mg/kg) to rats for periods of two to six weeks dramatically lowers circulating testosterone and dihydrotestosterone concentrations (Harmon *et al.*, 1976; Symons *et al.*, 1976; Purohit *et al.*, 1979; Rosenkrantz and Esber, 1980). CBN, administered chronically to mice (Dalterio, 1980) or rats (Purohit *et al.*, 1979), seems to be about as potent as Δ^9–THC. The magnitude of the decline in circulating testosterone speaks for an effect beyond what could possibly be due to decreased food intake; e.g., serum testosterone levels in rats receiving *ad lib* feeding and treated with Δ^9–THC (8 mg/kg) for 40 days were 1.78 ± 0.02 ng/ml, compared to 2.88 ± 0.11 in *ad lib* fed controls and 2.22 ± 0.16 in controls pair-fed with the THC group (Harmon *et al.*, 1976). Unfortunately, the design of most chronic studies did not include pair-feeding, or investigation of dose-response relationships, nor was the time between last cannabinoid administration and blood sampling always stated (exceptions are Maskarinec *et al.*, 1978b; Purohit *et al.*, 1979).

The diminished steroidal androgen levels in plasma are consistent with, and may be taken to explain, the regression of androgen target tissues. However, Fujimoto *et al.* (1979) reported an "anti-androgenic" effect of Δ^9–THC in Fischer rats without a concomitant decrease in circulating testosterone concentrations. Δ^9–THC, at oral doses of up to 50 mg/kg for three or seven weeks did not affect plasma hormone levels in mice; this was in contrast to CBN which depressed plasma testosterone (Dalterio, 1980). In Wistar rats, a dose of CME delivering 10 mg/kg Δ^9–THC has been reported to be much more active than the same dose of Δ^9–THC alone (*CME*: 160 ± 18; Δ^9–THC: 427 ± 23; *vehicle*: 452 ± 38 ng testosterone/ml). Δ^9–THC-induced dose-related increases in urinary 5α–androstane–3α, 17ß–diol sulfate and pregnanediol were also noted (Maskarinec *et al.*, 1978a and b).

Action on Testes

Chronic administration of Δ^9–THC or CME to rats or mice results in testicular weight changes of limited magnitude (0%–30%), and with considerable variability (Bloch *et al.*, 1978). Large cumulative doses tend to give transient modest increases in weight; moderate cumulative doses show weakly suppressive or no effects. It should be recognized that most of these studies have been in initially immature rather than adult rats; therefore it is the influence of marihuana on testis maturation that has been investigated. Cannabis extract has also produced marked degenerative changes in the testes of the toad (Dixit *et al.*, 1977).

Testes do not show a marked affinity for Δ^9–THC or its metabolites (Ho *et al.*, 1970; Ryrfeldt *et al.*, 1973; Martin *et al.*, 1976) but these are probably retained in cellular lipid depending on their degree of

TABLE 1

Effects of Repeated or Chronic Administration of Cannabinoids on Testes, Prostate and Seminal Vesicle Weights

Species	Strain	Age	Cannabinoid	Dose[(a)] (mg/kg/day)	Duration (days)
Rat	Fischer	100 g	[Δ^8–, Δ^9–THC CME]	[50 150]	28–119
Rat	Fischer	100 g	Δ^9–THC	50	[28 90, 180]
Rat	Fischer	100 g	Δ^9–THC	[10 50]	28–180
Rat				4	[28, 57 87, 180]
Rat	Fischer	Adult	CME	15, 75	77
Rat	S.D.	21 day	Δ^9–THC	10(3/wk)	28
Rat	S.D.	25 day	Δ^9–THC	20	70
Rat	Wistar	20 day	CME	90 ppm(e)	37
Rat	Wistar	Adult	Δ^9–THC	16	4

Reproduced from Bloch *et al.*, 1978, courtesy of Academic Press, Inc.
Effect expressed as increase (↑), no change (0), decrease (↓), or questionable effect (±)

(a) minimum dose giving consistent results in relation to higher dose(s) or over a period of time
(b) after 5 and 28 days: (↑); after 91 and 119 days: (0)
(c) after 180 days: 0
(d) after 28 and 57 days: (↓); after 87 and 180 days: (0)
(e) 50 ppm Δ^9–THC or approx. 5 mg Δ^9–THC/kg/day p.o.; for testes, effective dose approx. 270 ppm CME (Okey and Truant, 1975)

Route of Administration	Effect on: Testes	Prostate	Sem. Ves.	Reference
	(weight/kg of body weight)			
p.o.	↑ ± (b)	↓	—	Thompson *et al.*, 1973
p.o.	[↑ ↑	↓ 0] (h)	—	Rosenkrantz *et al.*, 1975
p.o.	[↑ ↑	0 ↓ ± (d)]	—	Rosenkrantz *et al.*, 1976
inhalation	[↓ ↓ ± (c)	↓ 0]	—	Rosenkrantz *et al.*, 1976
p.o.	↑ ±	↓	↓ (h,i)	Fujimoto *et al.*, 1978, 1979
i.p.	0	↓	0	Collu *et al.*, 1975
(not stated)	—	—	↓	Solomon and Shattuck, 1974
diet	↓	↓	↓	Okey and Truant, 1975
i.p.	0	0	0	Ling *et al.*, 1973

(f) equal to approx. 10 mg/kg/day injected peripherally (Collu, 1976)
(g) castrated with endpoint of testosterone stimulation of accessory reproductive organ weights
(h) effects reversible after cessation of treatment
(i) epididymal weight, seminal fluid volume and fructose content (↓) reversibly
(j) levator ani weight (↓)

TABLE 1 (CONTINUED)

Species	Strain	Age	Cannabinoid	Dose (a) (mg/kg/day)	Duration (days)
Rat	S.D.	[23 50 day]	Δ^9-THC	[20 µg 50 µg] (f)	7
Rat	W. Reed	20 day	Δ^9-THC	8	40
Mouse	Swiss-Albino	Adult	CME	70	45
Mouse	Swiss-Albino	Adult (g)	CME	200	?

lipophilia. Of interest is the preferential localization of ^{14}C-Δ^9-THC in epididymal fat in mice; twice as much is found there as in inguinal or perineal fat 30 min after i.v. injection (Rawitch *et al.*, 1979). Such storage would act as a local source of Δ^9-THC for an appreciable time (Kreuz and Axelrod, 1973).

The results of recent *in vitro* studies place one site of cannabinoid inhibitory action in the testes themselves. Δ^9-THC, CBN and other cannabinoids inhibited testosterone synthesis from endogenous or exogenous precursors during incubation with mouse or rat testicular tissue preparations or Leydig cell suspensions (Dalterio *et al.*, 1977, 1978; List *et al.*, 1977; Burstein *et al.*, 1978, 1979a; Harclerode *et al.*, 1979; Jakubovič *et al.*, 1979a and b; Dalterio, 1980). The results obtained by Dalterio *et al.* (1978) may be cited as an illustration. When mouse testes were incubated in buffer with 80 µM Δ^9-THC or CBN, with and without added human chorionic gonadotrophin (hCG), the amounts of testosterone synthesized (ng/ml of incubation medium) during a four-hour period were:

cannabinoid	*no hCG*	*hCG*
control groups	{71 ± 19 82 ± 17}	{517 ± 58 368 ± 27}
Δ^9-THC	70 ± 17	71 ± 16
CBN	45 ± 11	99 ± 10

Route of Administration	Effect on: Testes	Prostate	Sem. Ves.	Reference
	(weight/kg of body weight)			
intra-ventricular	0 0	↓ 0	0 0	Collu, 1976
p.o.	↓	—	—	Harmon *et al.*, 1976
i.p.	↓	—	↓ (h,j)	Dixit *et al.*, 1974
i.p.	—	↓	↓ (j)	Dixit and Lohiya, 1975

In this experiment only CBN lowered basal testosterone synthesis, but both CBN and Δ^9–THC impaired the response to added hCG. This *in vitro* depression of testosterone production is in agreement with, and explains, the drop in plasma testosterone levels following cannabinoid intake.

Other aspects of testicular metabolism have received attention, but none in penetrating depth. Mice treated i.p. *in vivo* with CME over a 45-day period (Dixit *et al.*, 1974) and dogs given CME s.c. for 30 days (Dixit *et al.*, 1977) exhibited moderate decreases in testicular weight, protein, RNA, and sialic acid (dog only) content, and in seminiferous tubule and Leydig cell diameters. Several marker proteins in rat testicular cells are decreased by chronic Δ^9–THC administration (Schwarz *et al.*, 1978). In addition to inhibiting protein synthesis, cannabinoids depress energy metabolism. ATP concentrations in testes from treated rats are decreased (Jakubovic and McGeer, 1977) and Δ^9–THC treatment *in vitro* may inhibit glycolysis (Husain and Lame, 1979). Some other cannabinoids and the metabolic derivatives of Δ^9–THC (i.e., 11–OH–Δ^9–THC, 8ß–OH–Δ^9–THC, CBN, CBD) are more active than Δ^9–THC in inhibiting steroid hormone formation and protein and nucleic acid synthesis (Jakubovič and McGeer, 1976, 1977; Burstein *et al.*, 1978; Dalterio *et al.*, 1978; Harclerode *et al.*, 1979; Jakubovič *et al.*, 1979a and b).

Mechanism of Action: Δ^9–THC may exert its effect by inhibiting cholesterol esterase activity, thereby decreasing the availability of

TABLE 2

Effects of Δ⁹–THC on Testosterone and LH Concentrations in the Plasma of Rats, Mice and Monkeys

Species	Strain	Dose(a) (mg/kg/day)	Duration (days)
Rat	Wistar	5(2/wk)	42
Rat	Wistar	50 (f)	7
Rat	Fischer	4 10	14 14
Rat	Fischer	1, 5	74
Rat	Fischer	10, 50	14, 28
Rat	S.D.	10(3/wk)	28
Rat	S.D.	20 μg 50 μg (b)	7
Rat	W. Reed	8	40
Rat	?	10	10
Rat	Wistar	5	S + 2(c)
Mouse	"Outbred"	50(3/wk)(g)	21, 49

Plasma FSH: 0 (Collu *et al.*, 1975; Dalterio *et al.*, 1978); ↑ (Rosenkrantz and Esber, 1980) after chronic administration

Plasma Prolactin: ↓ (Collu, 1976; Daley *et al.*, 1974); ↑ (Kramer and Ben-David, 1974; Bromley and Zimmerman, 1976) after acute administration

Animals were adults except 21-23-day-old rats (Symons *et al.*, 1976; Collu *et al.*, 1975). Effect expressed as increase (↑), no change (0), or decrease (↓). Table incorporates data from Bloch *et al.* (1978), with permission of publisher (Academic Press, Inc.).

Route of	Effect on:		
Administration	Test.	LH	Reference
i.m.	↓	↓	Symons *et al.*, 1976
p.o.	↓	—	Maskarinec *et al.*, 1978a
inhalation	↓	—	Rosenkrantz *et al.*, 1979
p.o.	↓	—	
p.o.	↑ (e)	—	Fujimoto *et al.*, 1979
p.o.	—	↑	Rosenkrantz and Esber, 1980
i.p.	—	↓	Collu *et al.*, 1975
intra-ventricular	— —	0 0	Collu, 1976
p.o.	↓	—	Harmon *et al.*, 1976
s.c.	↓ (d)	—	Purohit *et al.*, 1979
i.m.	↓	↓	Symons *et al.*, 1976
p.o.	0	—	Dalterio, 1980

(a) minimum dose giving consistent results in relation to higher dose(s) or over a period of time
(b) equal to approx. 10 mg/kg/day injected peripherally (Collu, 1976); 50 μg dose given to 50-day-old rats
(c) single injection of Δ^9–THC (S) with blood removal n hr (+n) later (e.g., S + 2 = blood collection 2 hr after Δ^9–THC injection)
(d) dihydrotestosterone also ↓; CBN as effective as Δ^9–THC
(e) 25 mg dose showed no increase
(f) CME more effective than Δ^9–THC
(g) testosterone ↓ with 50 mg CBN for 21 days
(h) ↑ post-treatment with CBD (*not* Δ^9–THC)

TABLE 2 (CONTINUED)

Species	Strain	Dose(a) (mg/kg/day)	Duration (days)
Mouse	"Outbred"	50	S + 4
Monkey	Rhesus	2.4	365
Monkey	Rhesus	100	90
Monkey	Rhesus	2.5	S + 6,12...

cholesterol for testosterone formation. Burstein and coworkers (1978, 1979a) demonstrated a dose-related inhibition of cholesterol esterase activity, and of basal and LH-stimulated testosterone synthesis in mouse Leydig cell preparations incubated with Δ^9–THC. ^{125}I–hCG binding, desmolase activity, mitochondrial cholesterol uptake, and conversion of pregnenolone to testosterone remained unaffected. Support for this locus of Δ^9–THC action comes also from the observations of an increase in testicular cholesterol esters four hours after oral Δ^9–THC administration to mice (Dalterio *et al.*, 1978), and a marked decrease on polyacrylamide gels in the intensity of one esterase isozyme band from rats given Δ^9–THC or CBD i.p. 24 hr before killing (Goldstein *et al.*, 1977).

Jakubovič *et al.* (1979a and b) also reported that incubation with cannabinoids produced a dose-related inhibition of hCG-or cAMP-stimulated testosterone production by Leydig cell suspensions. In contrast to the findings of Burstein *et al.* (1978), basal testosterone production was not inhibited, although higher cannabinoid doses suppressed hCG stimulated synthesis below basal levels. This group had earlier shown cannabinoid depression of protein, nucleic acid, and lipid synthesis in testis slices (Jakubovič and McGeer, 1976, 1977), and had suggested the locus of action to be on protein synthesis, with reduced synthesis underlying the reductions in both steroidogenesis and spermatogenesis. They now found in Leydig cell preparations a 10-fold difference in the effective dose inhibiting testosterone synthesis (1.5 μM) and protein synthesis (15 μM), leading Jakubovič to modify his earlier views and to suggest either inhibition of formation of a specific protein or separate sites of inhibitory action (Jakubovič *et al.*, 1979b). Confident interpretation of

Route of Administration	Effect on:		Reference
	Test.	LH	
p.o.	↓	↓	Dalterio *et al.*, 1978
diet	0	—	Sassenrath and Chapman, 1976
p.o.	(h)	↑	Rosenkrantz *et al.*, 1979
i.m.	↓	↓	Smith and Moore, 1976

the steroidogenesis data requires more rigorous studies of kinetics, titration of stimulant (e.g., hCG) with inhibitor (e.g., Δ^9–THC), and investigation of structure-activity relationships; these studies are still to be done.

Gonadotrophin Release

Relatively little investigative effort has been expended on cannabinoid-neuroendocrine relationships in males (Cicero, 1980). The available data indicate that cannabinoids act at the level of the hypothalamic-pituitary axis to affect gonadotrophin production (see Table 2), thereby exerting an indirect influence on testicular function. For example, in the careful studies of Symons *et al.* (1976), 5 mg Δ^9–THC, given i.m. chronically to weanling and acutely to adult rats, decreased plasma testosterone and LH concentrations by 25%–75%. Δ^9–THC also reduced the plasma LH increment normally seen after administration of exogenous LH releasing factor (LH-RH). In general, blood LH levels are diminished following acute or chronic CME or Δ^9–THC intake but cumulative large doses (0.28 to 1.4 g given to rats over 4 weeks) may have the opposite effect (Rosenkrantz and Esber, 1980). The effects are reversible. Harclerode *et al.* (1979), on the basis of results of Δ^9–THC-LH antagonism experiments, postulate that Δ^9–THC indirectly reduces cytochrome P–450 activity of testicular microsomes through suppression of pituitary LH release.

Pituitary FSH release may also be affected. Circulating FSH levels have been reported to be lowered in mice subsequent to acute Δ^9–THC treatment (Dalterio *et al.*, 1978). Chronic treatment with Δ^9–THC produced either no change in mice (Collu *et al.*, 1975) or increased plasma FSH levels in Rhesus monkeys (Rosenkrantz and Esber, 1980).

Circulating prolactin levels in male rats respond in a possible age-dependent manner to Δ^9–THC. In adults, i.p. injection of 2–10 mg Δ^9–THC led to a marked, abrupt but transient drop in serum prolactin concentrations (Kramer and Ben-David, 1974; Bromley and Zimmermann, 1976). A similar Δ^9–THC dose (16 mg/kg) increased prolactin levels in 36-day-old rats (Daley *et al.*, 1974). Intraventricular administration to 23-day-old rats increased pituitary prolactin content; no change was observed in 50-day-old rats (Collu, 1976). In a recent report, Kramer and Ben-David (1978) present evidence for Δ^9–THC interaction with the serotonergic and dopaminergic pathways controlling prolactin secretion.

The influence of cannabinoids on male sexual differentiation and development is discussed in Section 6.

Spermatogenesis

Crude extracts of marihuana and cannabinoids retard sperm maturation and increase the incidence of abnormal sperm. Oral or i.p. administration of CME or inhalation of marihuana smoke for periods of one to two months arrests spermatogenesis in dogs and mice, reduces epididymal sperm concentrations in rats, and produces seminal tubule degeneration (reviewed in Bloch *et al.*, 1978; Rosenkrantz and Hayden, 1979; Huang *et al.*, 1979). Epididymal sperm count gradually returns to normal upon cessation of cannabinoid exposure (Fujimoto *et al.*, 1978). Exposure to Δ^9–THC *in vitro* decreases sperm motility, respiration, and ATP content, and causes degenerative morphological changes (Shahar and Bino, 1974). The i.p. injection of Δ^9–THC or CBN for 5 days led to an increased incidence of abnormal sperm 35 days later in (C57BLxC3H)F_1 mice. The percentages of abnormal sperm in the various groups were: 0.6 mg mitomycin C/kg (a known mutagen), 9.2%; 5 and 10 mg Δ^9–THC/kg, 3.8% and 5.3% respectively; 10 and 25 mg CBN/kg, 3.3% and 8.6% respectively; and vehicle, 1.9% (Zimmerman *et al.*, 1979). CBD given i.p. was inactive in mice (Zimmerman *et al.*, 1979), but cannabichromene was active when inhaled by rats (Rosenkrantz and Hayden, 1979).

The Female Reproductive System

One of the earliest reports on any reproductive or endocrine effect of marihuana concerned female reproduction. It described the anti-oxytocic activity of CME in rat uterine strips (Bose *et al.*, 1963).

Acute Effects on Reproductive Activity (Table 3)

A single dose of Δ^9-THC will reduce blood LH concentrations and block ovulation in rabbits and Rhesus monkeys (Asch *et al.*, 1979a, b, c). The intensity and duration of the effect are dose-dependent, and the action is completely reversible and appears to be exerted at a suprapituitary site.

Nir *et al.* (1973) found the i.p. injection of Δ^9-THC into rats in early proestrus to suppress the preovulatory surge in plasma LH and to delay ovulation by 24 hr. CBD was inactive, but the synthetic dimethylheptyl derivatives of Δ^9-THC and CBD, the latter psychotropically inactive, are potent inhibitors of ovulation (Cordova *et al.*, 1980). In further work in the rat by the Lindner group, Δ^9-THC administered during the critical period for gonadotrophin release suppressed the proestrous rise in plasma LH, FSH, and prolactin levels (Ayalon *et al.*, 1977). LH-RH administration reversed these inhibitory effects of Δ^9-THC indicating a brain locus rather than a pituitary site of Δ^9-THC action. Ayalon *et al.* (1977) also reported evidence that supported an ovarian locus of Δ^9-THC action (see below).

In elegant studies, Tyrey (1978, 1980) demonstrated suppression of episodic LH secretion by Δ^9-THC in ovariectomized rats. A 62.5 μg/kg dose, given via an indwelling atrial cannula, sufficed to reduce the serum LH level 20 min later. The Δ^9-THC effect was dose-dependent, of limited duration, and reversed by LH-RH administration. An *in vitro* assay, in which hypothalamus and pituitary tissues are coincubated (Chakravarty *et al.*, 1979), showed less LH-RH in hypothalami from Δ^9-THC-treated rats (321 ng/hypothalamus from 10 mg/kg Δ^9-THC rats, $P<.01$) than from control animals in proestrus or diestrus (515 or 446 ng/hypothalamus respectively). These observations further support a brain locus of THC action.

In ovariectomized Rhesus monkeys, Smith *et al.* (1979a and b) and Besch *et al.* (1977) found a single intramuscular dose of Δ^9-THC to result in a precipitous drop in plasma LH and FSH levels. These reached minimum concentrations 6–12 hr after the Δ^9-THC injection, and then rapidly returned to basal levels. Duration of effect, but not magnitude, was related to dosage. The pituitary retained its responsiveness to LH-RH. A 2.5 mg Δ^9-THC/kg dose given to intact monkeys led to an anovulatory cycle. CBD was inactive (Besch *et al.*, 1978) and Δ^9-THC content accounted for the effects of CME (Smith *et al.*, 1979c).

Action on Ovary: Do Δ^9-THC and other marihuana constituents exert a direct effect on ovarian function? Serum progesterone concentrations in adult, cycling Rhesus monkeys did not respond to daily intake of 2.5 mg Δ^9-THC/kg during the secretory phase of the menstrual cycle, or

TABLE 3

Effects of Cannabinoids on Endocrine and Reproductive System of the Nonpregnant Female

Species	Strain	Age	Cannabinoid	Dose[(a)] (mg/kg/day)
Rat	Fischer	100 g	Δ^9–THC	2–50
Rat	CD	75 days	Δ^9–THC	1
Rat	Wistar	20 days	CME	360 ppm
		20 days	CME	200
		Adult[(b)]	CME	360 ppm
Rat	(not stated)	11 days	CME	120
Rat	(not stated)	Adult	CME	25
Mouse	Swiss-Albino	Adult	CME	40
Monkey	Macaca	Adult	Δ^9–THC	2.4

Effect expressed as increase (↑), no change (0), decrease (↓), or questionable effect (±). S + n = single injection with blood taken n hr (e.g., + 2, + 6) later; S + 1,2 ... sampling repeatedly for period of time. Table modified from Bloch *et al.* (1978) with permission of publisher (Academic Press, Inc.).

(a) minimum dose giving consistent results in relation to higher dose(s) over a period of time

(b) ovariectomized 6 weeks prior to cannabinoid administration

(c) see Table 1, footnote (e)

(d) antagonistic effect to estradiol-induced increase in uterine weight, glycogen, and water content

Duration (days)	Route of Adminis-tration[h]	Effect on: Uterus (wt/kg/body wt)	Ovary	Cycle Length	Reference
28–180	p.o.	0	0	—	Rosenkrantz *et al.*, 1975
14	i.p.	↑	—	—	Solomon *et al.*, 1976, 1977
8	diet	↓	—	—	Okey and Truant, 1975
	i.p.	0/↓ [c]	—	—	
15	diet	↓	—	—	
10	s.c.	↓ [d]	—	—	Chakravarty *et al.*, 1975a
64	i.p.	0 [e]	↓	absent	Dixit *et al.*, 1975
64	i.p.	↓ [e]	↓	absent	
365	diet	—	—	present	Sassenrath and Chapman, 1975

(e) decrease in uterine glycogen and in uterine and vaginal RNA and sialic acid
(f) after 14 and 28 days (↑); after 90 and 180 days (0)
(g) ovariectomized 3–5 weeks prior to cannabinoid administration
(h) CBD inactive (Besch *et al.* 1978) and CME as active as Δ^9–THC (Smith *et al.* 1979c)
(i) 70-day treatment schedule exhibited no effects
(j) Δ^9–THC given at 1200–1400 hr, proestrus; effect reversed by GnRH
(k) Weizman Institute bred, Wistar derived rats

TABLE 3 (CONTINUED)

Species	Strain	Age	Cannabinoid	Dose(a) (mg/kg/day)
Rat	Fischer	100 g	Δ^9–THC	10, 50
Rat	W.Wistar (k)	120 g	Δ^9–THC	5
Rat		Adult	Δ^9–THC	50
Rat		Adult (g)	Δ^9–THC	1–5
Rat	Holtzman	200 g	Δ^9–THC	5, 10
Rat	CD	300–400 g	Δ^9–THC	0.06–8
Rat	W.Wistar	200 g	Δ^9–THC	10
Mouse	A/J	11 wk	[CME Δ^9–THC, CME]	75
Rabbit	N. Zealand	3–4 kg	Δ^9–THC	1.25–5
Monkey	Rhesus	Adult (g)	Δ^9–THC	2.5
Monkey	Rhesus	Adult	Δ^9–THC	2.5
Monkey	Rhesus	Adult (g, h)	Δ^9–THC	0.625

Duration (days)	Route of Administration (h)	Effect on: LH	Other (in plasma)	Reference
14, 28	p.o.	↑ ± [f]	FSH: ↑ ±	Rosenkrantz, 1979
2S + 2	i.p.	↓	Cycle: Delay	Nir *et al.*, 1973
S + 6	i.v.	↓	PRL: ↓	Chakravarty *et al.*, 1975b
S + 1	i.v.	↓	—	Marks, 1972
10	i.p.	?	PRL: ↓	Chakravarty *et al.*, 1979
S + $^{1}/_{3}$, $^{1}/_{2}$...	i.v.	↓	—	Tyrey, 1978, 1980
S	i.p.	↓ [j]	PRL: ↓	Ayalon *et al.*, 1977
10 [i]	p.o.	—	[Progest. ↓ Cycle: Longer]	Kostellow *et al.*, 1980
S + 1,2...	i.m.	↓	Progest. 0	Asch *et al.*, 1979b and c
S + $^{1}/_{2}$,1...	i.m.	↓	PRL: ↓	Asch *et al.*, 1979a
Luteal	i.m.	—	Progest. 0	Asch *et al.*, 1979b
S + 6,12	i.m.	↓	FSH: ↓	Smith *et al.*, 1979b

of Δ^9–THC given with or without hCG during days 6–10 of the cycle (Asch *et al.*, 1979c). Rat luteal cells, incubated *in vitro* with cannabinoids and hCG, showed cannabinoid antagonism of hCG-stimulated progesterone formation. CBN and 7-OH-CBN, at lower concentrations (3.0–3.2 μM) than Δ^9–THC (16 μM), effected a greater reduction (55%–67%) than Δ^9–THC (39%). Δ^9–THC, but not CBN, decreased ^{14}C-cholesterol oleate hydrolysis by about 30% (Burstein *et al.*, 1979b). Inhibitory activities were small and dose-response relationships were not established.

The strongest evidence for a direct action of Δ^9–THC on ovarian function comes from Lindner's laboratories (Nir *et al.*, 1973; Ayalon *et al.*, 1977). A dose of 10 mg Δ^9–THC injected i.p. at 14:00 hr into proestrous rats blocked ovulation and diminished ovarian prostaglandin E content by 85%. Reversal of these effects was achieved by injection at 16:30 hr of 20 μg ovarian LH (oLH) per rat. The proestrous surge of LH is followed by increased follicular prostaglandin synthesis and accumulation (Bauminger *et al.*, 1975), a rise which is prevented by pentobarbital administration (Bauminger and Lindner, 1975). The amount of oLH required to reverse the THC effects (10 μg/rat) was four-fold that needed to counteract the pentobarbital inhibition (2.5 μg oLH/rat), suggesting thereby a direct action of Δ^9–THC on ovarian prostaglandin synthesis.

Chronic Administration and Long-Term Effects (Table 3)

CME administration i.p. to rats and mice for 64 days stopped ovarian function (Dixit *et al.*, 1975). The ovarian cycle ceased by day 30 of treatment; after 64 days, ovaries were smaller than in controls, and had many atretic follicles and reduced luteinization. Another study (Kostellow *et al.*, 1980) found no effect of CME or Δ^9–THC, at oral doses of up to 75 and 25 mg/kg/day, respectively, for 70 days, on estrous cycles or mating frequency in A/J mice. A regime of 8 days of identical treatment delayed entry into proestrus but did not prevent ovulation. At the highest dosage used, serum progesterone levels and mating frequency were reduced (Kostellow *et al.*, 1980). The contradictory results of Dixit *et al.* (1975) and of Kostellow *et al.* (1980) are not readily reconciled. Chronic Δ^9–THC treatment of intact adult rats with daily oral doses of 10 and 50 mg for 2 and 4 wk raised serum LH and FSH concentrations, effects not found with 3- and 6-mo treatment periods (Rosenkrantz and Esber, 1980). An earlier study using the same treatment regime failed to reveal any significant weight or morphological changes in uteri or ovaries (Rosenkrantz *et al.*, 1975). In two studies with primates, the menstrual cycles of 2 macaque monkeys were not affected by injection of 2.4 mg Δ^9–THC/kg/day for one year (Sassenrath and Chapman, 1975), and up to 300 mg CBD/kg/day for 90 days did not alter serum LH and FSH levels (Rosenkrantz and Esber, 1980).

Effect of Cannabinoids on Pregnant and Lactating Females

Pregnancy: Few cannabinoid effects have been described in female animals which are exclusively or primarily associated with pregnancy (cf. review by Bloch *et al.*, 1978).

In mice and rats, low or moderate doses of Δ^9–THC given by various routes during the entire pregnancy, or during selected periods only, were without effect on length of gestation, maternal viability, or maternal weight gain. Cumulative doses of 1 to 4 g/kg (!) Δ^9–THC prolonged pregnancy in rats by 2 to 3 days which, in view of normal birth weights, suggested delayed nidation rather than delayed parturition (Borgen *et al.*, 1971; Pace *et al.*, 1971). Large doses of Δ^9–THC will decrease or abolish the maternal weight gain normally seen in pregnancy. However, relative weight loss is not confined to the pregnant state. Other effects ascribed to exposure to large doses of Δ^9–THC or CME during pregnancy are hemoconcentration, increased red blood cell titers, and depletion of fat deposits.

Radioautographic studies showed corpora lutea of pregnant mice to concentrate ^{14}C–Δ^9–THC (Freudenthal *et al.*, 1972; Kennedy and Waddell, 1972). Such preferential uptake is confined to corpora lutea since Δ^9–THC localization in ovarian stroma and follicles was not marked in mice, and did not exceed that found in plasma of pregnant and nonpregnant rabbits (Agurell *et al.*, 1970), and dogs (Martin *et al.*, 1976). The localization in luteal tissue may indicate protein binding, with its physiological implications, or more simply reflect the lipid solubility of Δ^9–THC. This finding merits further studies with respect to species distribution and functional significance.

Another maternal (and nonmaternal) tissue localizing Δ^9–THC is adipose tissue. Release is relatively slow (Harbison and Mantilla-Plata, 1972) and adipose tissue may be viewed as a potential Δ^9–THC reservoir. A group of male and female chimpanzees smoking cannabis did not differ from nonsmokers with respect to pregnancy and fertility. The nine smokers had consumed 50 to 150 doses of 1–2 mg Δ^9–THC/kg during periods ranging from 48 to 535 days prior to mating (Grilly *et al.*, 1974).

Lactation: Lactation appears to be reduced by Δ^9–THC. Pups of rats injected s.c. with a cumulative dose of up to 1.2 g/kg Δ^9–THC during the 10th–16th days of pregnancy had a high neonatal mortality, which was relieved by cross-fostering the pups. This was ascribed to diminished milk reaching the newborn and indeed no milk was visible in the pups' stomachs (Borgen *et al.*, 1971; Pace *et al.*, 1971). The locus of action may involve inhibition (Chakravarty *et al.*, 1975b; Asch *et al.*, 1979c) or delay (Raine *et al.*, 1978) of prolactin production, presumably at a hypothalamic site (Raine *et al.*, 1978; Asch *et al.*, 1979c). The delayed rise in plasma prolactin subsequent to daily s.c. injection of 25 mg/kg Δ^9–THC into mice 13 days pregnant to 12 days postpartum may explain the depressed mammary gland growth and delayed maximum activity of mammary lipoprotein lipase observed concurrently in these studies (Raine *et al.*, 1978). Δ^9–THC also inhibits the suckling-induced release of prolactin in the lactating rat (Bromley *et al.*, 1978).

The emerging picture is one of Δ^9–THC acting at a neural level (dopaminergic and serotonergic hypothalamic-thalamic tracts) to either augment prolactin-inhibitory factor (PIF) release or oppose prolactin-releasing factor (PRF) release, thereby reducing plasma prolactin levels. This, in turn, inhibits mammary gland development, lipoprotein lipase activity and lactation, all requiring prolactin for sustained activity. However, a direct effect of cannabinoids on mammary gland metabolism may also be involved; mammary glands accumulate Δ^9–THC (Forney and Kiplinger, 1971; Freudenthal *et al.*, 1972; Kreuz and Axelrod, 1973). No effects on lactation were noted with low doses of Δ^9–THC (0.5–5 mg/kg) or the equivalent doses of CME in rats and mice (Keplinger *et al.*, 1973; Maker *et al.*, 1974), but ^{14}C–Δ^9–THC, administered to lactating squirrel monkeys, was found in low concentrations in both milk and suckling infants (Chao *et al.*, 1976).

Cannabinoids as Estrogen Agonists and Antagonists

Δ^9–THC and CME have actions both similar and opposite to those of estrogens on several target tissues of estrogens; they have been viewed as both estrogen agonists and antagonists. Is the locus of cannabinoid action at the same site as that of steroidal estrogens?

Most studies have been done on the uterus (Table 3). CME and Δ^9–THC generally decrease uterine weight and metabolism in rats and mice (Bloch *et al.*, 1978). Uterine weight, glycogen content, RNA, and sialic acid levels decline during cannabis administration. A series of papers by Chakravarty *et al.* (1975a, 1976), Chakravarty and Ghosh (1977) and Chakravarty (1980) reported CME to antagonize estradiol-stimulated weight gain, glycogen deposition, glycogen synthetase and phosphorylase activities. The uterotrophic effect of estradiol in suckling rats was delayed by CME (Chakravarty *et al.*, 1975a), and Δ^9–THC restored estradiol-suppressed plasma LH concentrations to their uninhibited levels (Marks, 1973).

In a recent study, Virgo (1979) found Δ^9–THC at 3–12 mg/kg/day to be without activity in three estrogen-sensitive systems. Δ^9–THC for 2 weeks s.c. failed to increase uterine weight, protein or glycogen content in ovariectomized mice, parameters which were increased two-to-six-fold by 2 μg/kg estradiol. Δ^9–THC did not reduce implantation frequencies as opposed to 150 μg estradiol/kg given on day 0 of pregnancy. Finally, Δ^9–THC, unlike 4.0 μg estradiol/kg, did not restore implantation in mice ovariectomized on day 1 of pregnancy. In ovariectomized Rhesus monkeys, 100 μg estradiol/day for 14 days resulted in maturation of the vaginal epithelium and proliferation of the endometrial glandular epithelium, but Δ^9–THC, 2.5 mg/kg/day, was without effect (Smith *et al.*, 1979a).

In some respects, however, cannabinoids mimic estrogen action: increased adrenal and pituitary weight, stimulation of ACTH secretion, altered prolactin production, reduced weights of testes, prostate and seminal vesicles, and (questionably) stimulation of mammary gland development. (One of the earliest "alerts" of cannabis as an estrogenic compound came from Harmon and Aliapoulios' (1972) observation of gynecomastia among 3 heavy marihuana users.) Solomon *et al.* (1976, 1977) found moderate doses of Δ^9–THC to be uterotrophic and stimulatory to uterine and vaginal epithelia in ovariectomized rats. No dose-response relationship was observed.

Cannabinoids have been studied for their capacity to bind to uterine and mammary gland cytosol and to displace estradiol from its receptors in these tissues. ^{14}C–Δ^9–THC, incubated with mouse uterine cytosol, sedimented on sucrose gradients as 4S and 10.4S peaks (Rawitch *et al.*, 1977); the validity of these findings has been questioned (Okey and Bondy, 1978; Virgo, 1979). In a thorough study, ^3H–Δ^9–THC bound to mammary gland and uterine cytosol exhibited only the nonspecific 4S binding peak with high capacity (not diminished by 10^3-fold concentration of cold Δ^9–THC or 10^5-fold estradiol) and low affinity (label removed by repeated charcoal treatment) (Okey and Bondy, 1978). The competition of cannabis resin, Δ^8–THC, Δ^9–THC, or 11–OH–Δ^9–THC at micromolar concentrations with ^3H–estradiol for binding sites in uterine or mammary gland cytosol from rats and mice is weak at best (Rawitch *et al.*, 1977; Shoemaker and Harmon, 1977) or absent (Okey and Truant, 1975; Okey and Bondy, 1977, 1978). In Rhesus monkey uteri, ^3H–Δ^9–THC binding was not saturable and was not displaced by unlabeled Δ^9–THC or several steroids; conversely, 2.8 μM Δ^9–THC did not displace 10 nM ^3H–estradiol bound to uterine cytosol, while 28 nM diethylstilbestrol produced 80% displacement (Smith *et al.*, 1979d). Hence, in monkey and human (Smith *et al.*, 1979d), as well as in rat and mouse, Δ^9–THC does not bind to an estrogen receptor.

One may conclude that some of the biological and metabolic activities of estradiol are also exerted by Δ^9–THC or, conversely, inhibited by Δ^9-THC, albeit at rather low orders of potency. It also seems established that the metabolic and molecular site of Δ^9-THC action is different from that of estradiol. A biologically or mechanistically meaningful pattern of Δ^9-THC-estradiol-17β equivalence or antagonism has yet to emerge. Hence, the discussion of the "estrogenicity" of Δ^9-THC seems unproductive.

3. ADRENAL CORTICAL SYSTEM IN ANIMALS

Cannabinoid Effects on Pituitary-Adrenal Axis

CME, Δ^9-THC, and other cannabinoids stimulate adrenal cortical activity, probably through increasing ACTH output (review in Bloch *et al.*, 1978). The *acute* response to cannabinoids is generally a prompt rise in plasma corticosteroid levels and decreased adrenal ascorbic acid levels (Dewey *et al.*, 1970; see Tables 4 and 5; note also that there are exceptions to this generalization). Doses of 2–20 mg Δ^9-THC to rats, usually administered i.p., are effective as acute stimulants. 11-OH-Δ^9-THC, Δ^9-THC and CBN, in this order of potency, rapidly increase plasma corticosterone levels in mice (Johnson *et al.*, 1978). The dose-response relationship for Δ^9-THC and CBN indicated a maximal 2.2–2.5-fold increase at 30 mg/kg. CBD may exert a lowering effect (Jacobs *et al.*, 1979). Since these acute effects can be abolished by hypophysectomy, pentobarbital, or dexamethasone administration, one major locus of action appears to be at the level of the CNS and pituitary, with cannabinoids acting as stressors (Barry *et al.*, 1973).

Cannabinoids and corticosteroids may interact at the brain and pituitary level (review in Bloch *et al.*, 1978). The amygdala, preoptic area, hypothalamus, and pituitary localize labeled Δ^9-THC but not in a manner strikingly different from that of other brain structures. The uptake of ^{3}H-corticosterone by the hippocampus of adult male rats was reduced after the i.p. injection of 9 mg Δ^9-THC, but increased with a 3 mg dose (Drew and Slagel, 1973). In contrast, Johnson *et al.* (1978) found Δ^9-THC to increase hippocampal uptake of ^{3}H-corticosterone in adrenalectomized mice. Several unanswered questions, e.g., specificity of uptake, blood-brain ratios, and metabolic differences between species make comparisons of these two reports premature. Δ^9-THC acutely stimulated ACTH release as judged by adrenal ascorbic acid depletion in rats (Dewey *et al.*, 1970).

The acute action of cannabinoids on the pituitary-adrenal axis is well illustrated by the study of Maier and Maitre (1975). Intraperitoneal injection of Δ^9-THC into adult male rats resulted in a five- to six-fold elevation of plasma corticosterone concentrations, a decrease in adrenal ascorbic acid and cholesterol ester content, and a two-fold rise in plasma free fatty acids. The same effects were obtained with Δ^8–THC, dimethylheptyl–Δ^{6a-10a}–THC and ACTH, but with differing dose-response curves and decay in plasma corticosterone and free fatty acid concentrations with time. Hypophysectomy abolished the adrenal effects; adrenalectomy did not prevent the plasma free fatty acid increase. The studies to date support a locus of Δ^9–THC action in the brain resulting in stimulation of ACTH production and release.

Chronic Δ^9–THC or CME administration to rats or mice, usually orally or by i.p. injection, has been carried out for 4–8 days or 25–180 days (see Tables 4 and 5). Such chronic treatments led to increased adrenal and decreased thymus weights (reviewed in Bloch *et al.*, 1978). These effects appear to be reversible (Dixit *et al.*, 1974). Daily intraventricular injections of 50 μg Δ^9–THC for 7 days into 50-day-old rats led to adrenal and pituitary hypertrophy and increased corticosterone secretion (Collu, 1976). Two studies failed to detect adrenal enlargement or thymic involution with prolonged cannabinoid administration (Birmingham and Bartova, 1976; O'Connell *et al.*, 1980). *In vitro* corticosteroidogenesis and ACTH responsiveness were not affected by chronic Δ^9–THC administration (Ling *et al.*, 1973; Birmingham and Bartova, 1976). A dose-dependent relationship between adrenal cortical responsiveness and cannabinoid intake is suggested by the elevated plasma corticosterone values found 24 hr after the last of 72 daily injections into male, adult rats: vehicle, 98 ng/ml; 1, 5, and 25 mg/kg Δ^9–THC, 94, 144, 145 ng/ml, respectively; and 3, 15, and 75 mg/kg CME, 114, 175, and 214 ng/ml, respectively (O'Connell *et al.*, 1980). Responsiveness to stress was reduced. Palermo Neto *et al.* (1975) found CME to potentiate estradiol stimulation of adrenal and pituitary weight gain and of corticosteroidogenesis. Progesterone abolished both the primary estradiol activity and its potentiation by CME.

There are conflicting reports on the appearance of tolerance to the adrenocortical effects of cannabinoids. Five- to 25-day schedules of i.p. injections of 2–20 mg Δ^9–THC/day to rats did not impair adrenal capacity to respond acutely to Δ^9–THC by a prompt rise in plasma corticosterone levels (Barry *et al.*, 1973; Pertwee, 1974; Palermo Neto *et al.*, 1975; Miczek and Dixit, 1980) or a rapid depletion of adrenal ascorbic acid (Dewey *et al.*, 1970; Dixit *et al.*, 1975). However, in another study with rats (Birmingham and Bartova, 1976) an acute eight-fold rise in plasma corticosterone on day 1 of treatment decreased to a two-fold rise by day 8. Tolerance was also observed in mice after a 5-day treatment schedule (Pertwee, 1974) or one extending from 4 to 42 days (Miczek and Dixit, 1980). However, the "protection" against the stress of acute CME or Δ^9–THC injection did not extend to the stress of immobilization (Pertwee, 1974).

Species other than rats and mice have received little investigative

TABLE 4

Effects of Cannabinoids on Adrenal, Thymus and Pituitary Weights, and Adrenal Ascorbic Acid Content

Species	Strain	Age	Sex	Cannabinoid	Dose(a) (mg/kg/day)	Duration (days)
Rat	Fischer	100 g	M,F	Δ^8,Δ^9–THC CME	10 30	28–119
Rat	Fischer	100 g	M,F	Δ^9–THC	10	28–180
Rat	Fischer	100 g	M,F	Δ^9–THC Δ^9–THC	10 4	13–180 13–180
Rat	S.D.	21 day	M	Δ^9–THC	10(3/wk)	28
Rat	Wistar	Adult	M	Δ^9–THC	16	4
Rat	(not stated)	Adult	F	CME	25	64
Rat	Wistar	70 day	F(d)	CME	20	25
Rat	Albino	100 g	M	Δ^9–THC	18	15
Rat	S.D.		M	Δ^9–THC	5	5
Rat	Wistar	Adult	M	Δ^9–THC	20	8
Rat	S.D.	23 day 50 day	M	Δ^9–THC	20 μg (f) 50 μg (f)	7

Effects expressed as increase (↑), no change (0), or decrease (↓). Reproduced from Bloch *et al.* (1978), with permission of publisher (Academic Press, Inc.).

(a) minimum dose giving consistent results in relation to higher dose(s) or over a period of time

(b) increase at 50 mg dose after 91 days administration

(c) increase after 180 days administration of 10 mg to females only

Route of Administration	Adrenal (wt/body wt)	Thymus (wt/body wt)	Adrenal asc. acid	Pituitary (wt/b.wt)	Reference
p.o.	↑	—	—	↑	Thompson *et al.*, 1973(b)
p.o.	↑	0	—	↑ ± (c)	Rosenkrantz *et al.*, 1975
p.o. inhalation	↑	—	—	—	Rosenkrantz and Braude, 1976
i.p.	0	0	—	0	Collu *et al.*, 1975
i.p.	↑	↓	—	—	Ling *et al.*, 1973
i.p.	↑	↓	↑	—	Dixit *et al.*, 1975
i.p.	↑	—	—	↑	Palermo Neto *et al.*, 1978
i.p.	↑	—	0	—	Biswas *et al.*, 1976 (e, h)
i.p.	↑	—	↓	—	Dewey *et al.*, 1970 (h)
i.p.	0	0	—	0	Birmingham and Bartova, 1976
intraventricular	0 ↑	— —	— —	0 ↑	Collu, 1976

(d) ovariectomized at 60 days of age
(e) neutral lipid content, Δ^5–3β–hydroxysteroid dehydrogenase and glucose–6–phosphate dehydrogenase activities increased
(f) equal to approx. 10 mg/kg/day injected peripherally (Collu, 1976)
(g) plasma free fatty acid concentrations declined
(h) depletion of adrenal ascorbic acid after *single, acute* Δ^9–THC administration

TABLE 4 (CONTINUED)

Species	Strain	Age	Sex	Cannabinoid	Dose(a) (mg/kg/day)	Duration (days)
Mouse	Tuck No. 1	[21 day Adult	F M]	CME	100	5
Mouse	Swiss-Albino	Adult	M	CME	70	45
Mouse	Swiss-Albino	Adult	F	CME	40	64
Guinea Pig	Eng. short h.	Adult	M	Δ^9–THC	3	180
Monkey	Rhesus	Adult	M,F	Δ^9–THC	15	28

Route of Administration	Adrenal	Thymus	Adrenal asc. acid	Pituitary (wt/b.wt)	Reference
	(wt/body wt)				
s.c.	—	↓	—	—	Pertwee, 1974
i.p.	↑	↓	—	—	Dixit *et al.*, 1974
i.p.	↑	↓	↓	—	Dixit *et al.*, 1975
i.p.	0	—	—	—	Huy *et al.*, 1975 (g)
i.v.	—	↓	—	—	Thompson *et al.*, 1974
p.o.	—	0	—	—	

TABLE 5

Effects of Cannabinoids on Corticosteroid Production

Species	Strain[a]	Cannabinoid	Dose (mg/kg/day)
LONG-TERM ADMINISTRATION			
Rat	Wistar	CME	20
Rat	S.D.	Δ^9–THC	20 µg[c] 50 µg[c]
Rat	"Albino"	Δ^9–THC	8
Rat		Δ^9–THC	2
Rat	Wistar	Δ^9–THC	20[d]
Rat	Charles R.	Δ^9–THC	10
Rat	Fischer	Δ^9–THC, CME	5, 3
Rat	S.D.	Δ^9–THC	20
Mouse	Tuck No. 1	CME Δ^9–THC	500 10

Plasma corticosteroid response expressed as increase (↑), no change (0), or decrease (↓). Minimum effective doses listed. Table modified from Bloch *et al.* (1978), with permission of publisher (Academic Press, Inc.).

(a) all subjects were adult males except in Palermo Neto *et al.* (1975) (70-day male and female rats) and in Collu (1976) (see footnote (c))

(b) corticosteroid determined is usually corticosterone. PLASMA SAMPLE FOR CORTICOSTEROID DETERMINATION OBTAINED USUALLY WITHIN 2 HR AFTER "CHALLENGE" OR SINGLE DOSE OF CANNABINOID. Elevation of plasma corticosteroid level by cannabinoid inhibited or abolished by hypophysectomy (Kubena *et al.*,

Duration (days)	Route of Administration	Plasma Corticosteroid Response[b]	Reference
25	i.p.	↑	Palermo Neto *et al.*, 1975
7	intra-ventricular	0	Collu, 1976
8	i.p.	↑	Kubena *et al.*, 1971
8	i.p.	↑	Barry *et al.*, 1972
8	i.p.	↑	Birmingham and Bartova, 1976
21	i.p.	↑	Mitra *et al.*, 1977
72	p.o.	↑	O'Connell *et al.*, 1980
1–42	i.p.	↑ (e)	Miczek and Dixit, 1980
5	s.c.	0	Pertwee, 1974

1971; Maier and Maitre, 1975), dexamethasone (Kokka and Garcia, 1974), pentobarbital (Barry *et al.*, 1972), pentobarbital + morphine (Kubena *et al.*, 1971)

(c) 20 μg injected intraventricularly to 23-day-old males, 50 μg to 50-day-old males. Both doses approximated 10 mg/kg/day injected peripherally (Collu, 1976)

(d) increase at 3 mg dose injected i.p. for 2 days; no response after 8-day regime

(e) tolerance developed by day 4 after administration

TABLE 5 (CONTINUED)

Species	Strain[(a)]	Cannabinoid	Dose (mg/kg/day)
SINGLE DOSE ADMINISTRATION			
Rat	"Albino"	Δ^9–THC	1
Rat		Δ^9–THC	1
Rat	S.D.	[Δ^8–, Δ^9–THC DMPH]	30
Rat	S.D.	Δ^9–THC	10
Rat	Wistar	Δ^9–THC	3
Rat	Wistar	[Δ^9–THC CBD]	5
Rat	Charles R.	Δ^9–THC	10
Rat	(not stated)	Δ^9–THC	30
Mouse	Tuck No. 1	Δ^9–THC	20
Mouse	ICR	[Δ^9–THC, CBN 11–0H–Δ^9–THC]	[30 3]

Duration (days)	Route of Administration	Plasma Corticosteroid Response[(b)]	Reference
single	i.p.	↑	Kubena *et al.*, 1971
single	i.p.	↑	Barry *et al.*, 1972
single	i.p.	↑	Maier and Maitre, 1975
single	i.p.	↑	Kokka and Garcia, 1974
single	i.p.	↑	Birmingham and Bartova, 1976
single	i.p.	$\left[\begin{smallmatrix}0\\ \downarrow\end{smallmatrix}\right]$	Jacobs *et al.*, 1979
single	i.p.	↑	Mitra *et al.*, 1977
single	i.p.	↑	Bromley and Zimmerman, 1976
single	i.p.	↑	Pertwee, 1974
single	s.c.	↑	Johnson *et al.*, 1978

attention. CME or Δ^9-THC did not affect adrenocortical activity in rabbits (Maier and Maitre, 1975; Thompson *et al.*, 1975) or guinea pigs (Huy *et al.*, 1975). Urinary cortisol levels and responsiveness of macaque monkey adrenals to ACTH did not change during a one-year regime of oral dosage with 2.4 mg Δ^9-THC daily (Sassenrath and Chapman, 1975). An exception to these generally negative observations was thymus involution following the i.v. injection of 15 mg Δ^9-THC/kg/day for 4 wk into adult Rhesus monkeys (Thompson *et al.*, 1974). It is hard to assess just how meaningful these reports are: handling alone may have caused maximal adrenal stimulation; cannabinoid doses were low, and the published studies are few.

Direct Effects on Adrenal Cortex

Cannabinoids exert a direct and apparently inhibitory action on adrenocortical activity. The variations in the time-course of the steroidogenic and lipolytic responses to different cannabinoids and to ACTH (Maier and Maitre, 1975) have been mentioned above. Δ^9-THC, CBN or CBD added to cultured mouse adrenal tumor cells largely abolished cellular responsiveness to subsequent ACTH stimulation (Carchman *et al.*, 1976; Warner *et al.*, 1977). CBD was most active, with half-maximal inhibition of ACTH-stimulated steroidogenesis at 0.3 μM compared to 100 μM for Δ^9-THC and 20 μM for CBN (Warner *et al.*, 1977). Further, CBD depressed basal levels of corticosteroid production in this *in vitro* system. The inhibition of steroidogenesis was not the result of a generalized diminution of cell function or viability. The site of cannabinoid action on steroidogenesis seems to be between cAMP and pregnenolone production, since the stimulation of steroidogenesis by ACTH, cholera toxin, and cAMP, but not by added pregnenolone, was counteracted by Δ^9-THC (Warner *et al.*, 1977).

The adrenal cortex of mice, rats, rabbits, and dogs takes up ^{14}C- or ^{3}H-labeled Δ^9-THC *in vivo* to achieve tissue:plasma ratios of 2 to 6 within 20 min to 3 hr after administration (reviewed in Bloch *et al.*, 1978). In rabbits, Agurell *et al.* (1970) noted a tissue:plasma ratio >1 as late as 3 days after Δ^9-THC administration. These data suggest selective Δ^9-THC retention in the adrenal cortex, as in the corpus luteum (see Section 2), and raise the possibility of localized action. Entry of the highly lipophilic Δ^9-THC into adrenocortical mitochondrial lipids with subsequent inhibition of steroidogenesis may be visualized. Δ^9-THC apparently interacts with glucocorticoids in regulating macromolecular synthesis in responsive cells (Wrenn and Friedman, 1978; Carchman *et al.*, 1979). Understanding of both direction and mechanism of this interaction awaits further work.

4. OTHER ENDOCRINE SYSTEMS IN ANIMALS

CME inhibits ^{131}I release from rat thyroid (Lomax, 1970), and

Δ^9–THC, 10 mg/kg, reduces rat plasma *thyroxine* levels by 20%–30% (Nazar *et al.*, 1977). These actions are overcome by the subsequent injection of TSH, or by placing electrolytic lesions in the caudal hypothalamus, suggesting a site of cannabinoid action in the CNS. Chronic exposure of rats to marihuana smoke (equivalent to 2 and 4 mg Δ^9–THC/kg) or to oral Δ^9–THC (10 mg/kg) lowers serum thyroxine and triiodothyronine levels by 14%–25% (Rosenkrantz and Esber, 1980). Serum thyroxine concentrations in adult Rhesus monkeys were lowered by Δ^9–THC but increased by CBD given for 90 days (Esber *et al.*, 1976, 1979). However, the changes were minimal and not related to dose. It seems that in common with other endocrine glands regulated by the brain and pituitary, the thyroid is also affected by cannabinoids at moderate doses, and one locus of action is apparently in the brain.

Plasma *growth hormone* levels did not respond to oral doses of 2 to 50 mg Δ^9–THC/kg given to adult rats over a 14- to 180-day period (Rosenkrantz and Esber, 1980). Immature rats showed a 50%–66% drop (Collu *et al.*, 1975), but with direct injection of Δ^9–THC into the ventricles of the brain, growth hormone concentrations in both plasma and pituitary gland rose (Collu, 1976).

Moderate doses of Δ^9–THC injected chronically (up to 20 mg/kg daily for 1–4 wk) into rats exerted variable effects on adrenal *catecholamine* content and synthesis (Mazurkiewicz-Kwilecki and Filczewski, 1973; Biswas *et al.*, 1976; Miczek and Dixit, 1980). Conflicting reports on the effects of Δ^9–THC on the synthesis, concentration, and metabolism of neurotransmitters in brain (epinephrine, norepinephrine, serotonin, dopamine) have appeared (Schildkraut and Efron, 1971; Sofia *et al.*, 1971; Mazurkiewicz-Kwilecki and Filczewski, 1973; Ho *et al.*, 1974; Collu, 1976; Johnson and Dewey, 1978; Taylor and Fennessy, 1979; Miczek and Dixit, 1980). These are beyond the scope of this review. The *pancreas* concentrates ^{14}C–Δ^9–THC but the cell type involved was not specified (Kennedy and Waddell, 1972).

In general, almost no studies on the response of endocrine systems to cannabinoids, other than those involving the pituitary, steroidogenic tissues, and thyroid, have appeared in the literature. Our ignorance is nearly absolute.

5. REPRODUCTIVE AND ENDOCRINE EFFECTS OF CANNABIS IN HUMANS

Reproduction

Males

Harmon and Aliapoulios (1972) observed gynecomastia in three

23–26-yr-old marihuana smokers and Kolodny *et al.* (1974) noted oligospermia (35% of subjects) and lowered plasma testosterone levels in twenty 18–28-yr-old chronic smokers. These initial observations provided much of the impetus for studies on marihuana effects on the male reproductive system. The overall results of these studies indicate an effect on spermatogenesis but no influence on circulating hormone levels.

Fewer spermatozoa are found in the ejaculate of cannabis smokers. Five young males who smoked an amount of marihuana that increased from 1 to 8 cigarettes/day over a 2 wk period and then stabilized at an average consumption of 7 to 20 cigarettes/day (140–400 mg Δ^9–THC/day) for 2 wk demonstrated sperm count reductions of 30%–70% (Hembree *et al.*, 1976). Later, Hembree *et al.* (1979) reported that smoking for 4 wk (120–400 mg Δ^9–THC/day) was associated with decreased sperm count and motility, and increased percentage of abnormal morphology, during the last smoking and first two postsmoking weeks. The authors interpreted these findings as indicating perturbation of spermiogenesis by cannabis.

With respect to hormone production (see Table 6), Kolodny *et al.* (1976) reported that acute marihuana smoking (20 mg Δ^9–THC/cigarette) by chronic users resulted 2–3 hr later in decreased circulating testosterone and LH concentrations, both when marihuana was smoked during a period of abstinence and during one of steady consumption. In all other studies, plasma testosterone (Mendelson *et al.*, 1974, 1976, 1978; Cushman, 1975; Schaefer *et al.*, 1975; Coggins *et al.*, 1976; Hembree *et al.*, 1976) and LH (Mendelson *et al.*, 1978) concentrations in chronic smokers and nonsmokers were found to be the same.

In a detailed survey, Coggins *et al.* (1976) found testosterone levels to be within similar limits among 40 nonsmokers and 40 matched marihuana users who smoked at least 3 times a week for 10 yr or more. A subgroup of 13 males consuming a minimum of 10 cigarettes/day (equivalent to 26–74 mg Δ^9–THC/day) had plasma testosterone concentrations of 5.22 ± 1.76 ng/ml as compared to 5.50 ± 1.18 among paired controls. Both nonsmokers and heavy smokers fathered an average of 2.6 children. Mendelson *et al.* (1978) also could not discern any significant relationship between marihuana smoking and plasma testosterone and LH concentrations in 13 smokers in a study in which testosterone concentrations in plasma samples taken hourly over each of three 24-hr periods were integrated and compared: the day preceding a 21-day smoking regime, the last day of smoking, and the third day postdrug. Average daily consumption was 2–7 cigarettes (equivalent to 40–140 mg Δ^9–THC) which rose to 3–20 cigarettes (60–400 mg Δ^9–THC) on the last smoking day. Circadian rhythms of hormone levels were also not altered and no relationship between testosterone levels and intensity of marihuana consumption could be established.

Gynecomastia is occasionally found in marihuana smokers (Harmon and Aliapoulios, 1972, 1974; Cates and Pope, 1977; Olusi, 1980). No epidemiological evidence exists to suggest marihuana consumption as a cause of gynecomastia. Marihuana does not affect plasma prolactin levels in human males (Kolodny *et al.*, 1974; Lemberger *et al.*, 1975).

What conclusions, if any, can be drawn from these studies? Several of the published reports are difficult to interpret because of inadequate experimental designs, e.g., lack of appropriate control groups, insufficient sampling frequency, sample size, or heterogeneity of cannabis smoked. Oligospermia may be a real consequence of cannabis smoking; its onset, duration, and intensity are probably a function of aggregate marihuana consumption over a period of time. An understanding of this phenomenon would require studies extending over several spermatogenic cycles. Chronic marihuana intake is not associated with decreased plasma testosterone and LH levels. The work of Kolodny *et al.* (1976) and Jones (1976), and the results of rodent studies, suggest that acute effects may exist and should be further investigated. I am inclined to adapt the thesis of Mendelson *et al.* (1978) on steroidogenesis and spermatogenesis to the question of gynecomastia: "Considering the very widespread use of marihuana by adult males for a period approaching a decade, if marihuana did affect [mammary tissue growth], a large number of clinical case reports of [gynecomastia] would have been forthcoming."

Females

The available knowledge on the reproductive system in women smokers of cannabis was summarized by Adamec (1976): ". . . . a general comment . . . concerning the lack of information on women who smoke. Dr. Perez-Reyes mentioned that the rate and pattern of metabolism of a contraceptive [^{3}H–norethynodrel] administered i.v. to 5 young women are unaffected in women who have smoked 0.5–5 marihuana cigarettes/week (Perez-Reyes *et al.*, 1976). I am making a request for more information on female cannabis smokers." This statement holds equally true in the early 1980s.

Adrenal Cortex

In humans, cannabinoid intake did not alter adrenocortical activity or function (Hollister, 1969; Hollister *et al.*, 1970; Kolodny *et al.*, 1974) (Table 6). Hollister (1969) and Hollister *et al.* (1970) emphasized the contrast between the responsiveness of rat adrenal corticosteroid secretion and the lack of response of human adrenals to comparable cannabinoid doses. Benowitz *et al.* (1976) reported diminished plasma cortisol in Δ^9–THC-treated males after insulin-induced hypoglycemia.

TABLE 6

Effects of Marihuana Smoking on Plasma Testosterone, LH and Cortisol (F) Levels and on Spermatogenesis in Humans

Group	N	Dose (cig./day)	Duration
1	13	1 3	S + 2, 3 9 wk(a)
2	12	1	S + 1.5
3	12 15	1–3.5 1.5–8	3 wk
4	13	2–7	3 wk
5	6	Δ^9–THC	2 wk
6	9	Δ^9–THC	S + 3
7	89	CME	S + 1.5, 5
8	20	1–>2	>6 mo
9	38	⩾3x/wk	10–28
10	30	7 (1–24)	7–37 yr

All subjects were experienced male smokers. Effect expressed as decrease (↓), no change (0), or questionable (±). N = number of subjects. S + 1.5, S + 3 etc. = single consumption of cannabinoids with blood sampling 1.5, 2, 3, or 5 hr later. Test. = testosterone, LH = luteinizing hormone, F = cortisol or 17-hydroxycorticosteroids. Adapted from Bloch *et al.* (1978) with permission of publisher (Academic Press, Inc.).

Groups 5, 6, 7 — oral administration of Δ^9–THC or CME
Group 5 — 3 ± 0.5 mg Δ^9–THC/kg body weight/day; given every 4 hr in oil. Cortisol (↓) only at 1 hr post-insulin (see text)

	Effect on:		
Test.	LH	F	Reference
↓	↓	—	Kolodny *et al.*, 1975, 1976
↓	↓	—	
0	—	—	Schaefer *et al.*, 1975
0	—	—	Mendelson *et al.*, 1974
0	—	—	
0	0	—	Mendelson *et al.*, 1978
—	—	↓ ±	Benowitz *et al.*, 1976
—	—	0	Hollister, 1969
—	—	0	Hollister *et al.*, 1970
↓	—	0	Kolodny *et al.*, 1974
0	—	—	Coggins *et al.*, 1976
—	—	0	Cruickshank, 1976

Group 6 — 0.35 to 0.65 mg Δ^9–THC/kg in aqueous media, (N = 10). Same response with 1.0–2.5 mg synhexyl /kg

Group 7 — administered CME equal to 0 (N = 17), 0.18–0.30 (N = 15), 0.35–0.53 (N = 36) or >0.53 mg Δ^9–THC/kg(N = 22)

Groups 8, 9, 10— surveys of chronic marihuana smokers

(a) 8-wk smoking period plus 1-wk abstinence

TABLE 6 (CONTINUED)

Group	N	Dose (cig./day)	Duration
8	20	1->2	>6 mo
11	16	7–20	4 wk

However, others found that smoking marihuana did not impair adrenocortical reactivity to ACTH (Perez-Reyes *et al.*, 1976). A group of 30 adult male smokers did not differ from nonsmokers in their excretion of the major urinary metabolites of cortisol (Cruickshank, 1976), but the intensity and duration of cannabinoid intake varied greatly: the men had smoked 7 to 37 yr, 1 to 24 cigarettes/day, with Δ^9–THC content of 0.7%–10.3%.

Other Endocrine Systems

Circulating thyroxine levels were not affected by chronic smoking of cannabis (Kolodny *et al.*, 1974; Cruickshank, 1976). A single 6 mg Δ^9–THC dose, given i.v. to males, impaired glucose tolerance and increased plasma growth hormone levels (Hollister and Reaven, 1974). Growth hormone (GH) response to insulin was less in marihuana smokers given Δ^9–THC (210 mg Δ^9–THC/day) in capsule form every 4 hr for 2 wk: the predrug concentration of GH was 52.6 ± 8.7 ng/ml, whereas after Δ^9–THC it was 18.8 ± 6.7 ng/ml (Benowitz *et al.*, 1976). Two of four daily smokers had an altered postdrug glucose-tolerance curve, with changes in plasma insulin concentrations paralleling those of plasma glucose (Podolsky *et al.*, 1971).

6. DEVELOPMENT

Placental Transfer of Cannabinoids

Δ^9–THC is transferred to a limited extent across the placenta to the fetus. Autoradiographic exposures of mounted whole body sections of 12–17 day pregnant mice injected with ^{3}H– or ^{14}C–Δ^9–THC revealed

Effect on: Spermatogenesis	Reference
↓	Kolodny *et al.*, 1974, 1976
↓	Hembree *et al.*, 1976, 1979

weak activity in fetal and placental tissues (Freudenthal *et al.*, 1972; Kennedy and Waddell, 1972; Ryrfeldt *et al.*, 1973). Quantitative time-distribution studies also showed a distribution differential between mother and fetus in rats (Pace *et al.*, 1971; Vardaris *et al.*, 1976), mice (Harbison and Mantilla-Plata, 1972; Harbison *et al.*, 1977), dogs (Martin *et al.*, 1977), and hamsters (Idänpään-Heikkilä *et al.*, 1969). Pace *et al.* (1971) injected $^{14}C-\Delta^9-THC$ i.v. into pregnant rats and found that one hour later, on a wet weight basis, placental cotyledons contained 50% to 60% as much activity as found in maternal tissues and two- to three-fold as much as in the fetus. More radioactivity per unit weight was found in the fetuses plus placentas at 18 or 20 days than at 13 or 15 days of pregnancy.

In timed transfer studies, Harbison and Mantilla-Plata (1972) and Harbison *et al.* (1977) demonstrated low but persistent levels of radioactivity in 14–15-day fetuses of mice injected i.p. or i.v. with $^{14}C-\Delta^9-THC$. At least 80% of the injected activity remained in the mother. Fetal radioactivity exhibited an experimental decay curve during the 48-hr postinjection period similar to those of maternal liver, kidney and plasma, and appeared to be a function of maternal plasma levels. The placenta, in contradistinction, retained its radioactivity at a steady level during the second postinjection day. After i.v. injection 30 min before sacrifice (Harbison *et al.*, 1977), approximately 40% of fetal radioactivity consisted of unidentified polar material, perhaps conjugates, 20% of $11-OH-\Delta^9-THC$, 8% of "dihydroxy-Δ^9-THC" and only 4% of unmetabolized Δ^9-THC. Placental tissue had a similar distribution.

A brief note reported placental passage of labeled Δ^9-THC in

6- 15-day pregnant hamsters sacrificed at intervals of up to 24 hr after drug administration (Idänpään-Heikkilä *et al.*, 1969). More radioactivity was found in the fetus than in maternal plasma, with 50% of the activity being unchanged Δ^9–THC.

It is seen that Δ^9–THC crosses the placenta to the fetus in mice and rats. A concentration gradient exists, with cannabinoid radioactivity of mother > placenta > fetus. Placental uptake of Δ^9–THC exceeds that of the fetus and release is slow. This may be viewed as a restriction in Δ^9–THC transfer into the fetus, but also makes the placenta a prolonged source of Δ^9–THC for the fetus. Since mice and rats rapidly metabolize Δ^9–THC, the nature of the cannabinoids crossing the placenta needs to be determined; predominantly oxygenated metabolites have been isolated from the mouse fetus. Species differences may exist and must be recognized. If the Idänpään-Heikkilä *et al.* (1969) work on Syrian golden hamsters is confirmed, a species with fetal uptake of Δ^9–THC will have been described. The yolk-sac placenta plays a more important role in rodent gestation than in primate pregnancy. Therefore, maternal cannabinoid transfer to the embryo and fetus in rodents may exhibit different characteristics from those predicted for humans and their chorioallantoic placenta. Rates of cannabinoid transport and metabolism by the placenta as a function of gestational age must also be determined.

Developmental Toxicity

The teratogenic expression of a noxious agent is usually dependent on the agent reaching the embryo during organogenesis. During earlier stages of development or at higher concentrations, drugs tend to be lethal, and later, to be growth-retarding. The nature of deformity depends on the temporal coexistence between active concentrations of the agent or metabolite and a susceptible molecular or metabolic process of differentiation. Within this frame of reference, the effects of marihuana on embryonic and fetal survival, growth and development are summarized in Table 7, and some of the details are considered in the following sections.

Embryonic and Fetal Survival

The administration of Δ^9–THC or CME to rats, mice, or rabbits, by different routes, in doses of Δ^9–THC equivalent to 25 mg/kg/day or greater, during the first two-thirds of gestation, is associated with increased fetal and embryonic mortality, i.e., increased resorption and decreased litter size (review by Bloch *et al.*, 1978, 1979; Rosenkrantz *et al.*, 1978; Rosenkrantz and Hayden, 1979; Sofia *et al.*, 1979; Kostellow *et al.*, 1980). There are reports to the contrary (Pace *et al.*, 1971; Mantilla-Plata *et al.*, 1973; Joneja, 1976). Later administration appears either not to be lethal or to have been insufficiently studied. The critical period for embryo deaths through oral cannabinoid ingestion has been placed at 6–7 days for mice and 7–9 days for rats (Rosenkrantz and Hayden, 1979), at 8 days for hamsters (Joneja, 1977a), and through i.p. injection, at 8–9 days for mice (Harbison and Mantilla-Plata, 1972).

The following brief summaries of selected studies are cited to amplify the data presented in Table 7 and to illustrate the diversity of experimental protocols abounding in this field. Δ^9–THC given at 100 mg/kg/day in olive oil s.c. to Long-Evans rats during days 1–20 of gestation reduced litter size significantly (Borgen *et al.*, 1971). In contrast, similar treatment (100 mg/kg in propylene glycol) administered s.c. to 6–15-day pregnant Charles River rats was ineffective (Banerjee *et al.*, 1975). Conceivably, differences in the Δ^9–THC solvent vehicle, period of injection and strain used may each have contributed to the divergent results obtained. A dose of 200 mg Δ^9–THC/kg/day in saline injected i.p. into pregnant Swiss-Webster mice on gestational days 8 and 9 induced a 68% resorption frequency; on days 10 and 11, 34%; and on days 12 and 13, 27% (Harbison and Mantilla-Plata, 1972). On the other hand, 300 mg/kg given as a single dose was markedly embryocidal on gestational days 8, 10, 12, 14, or 16 (40%–80% resorption rate) (Mantilla-Plata *et al.*, 1975). The 9-day span of effective embryotoxicity of the 300 mg dose may indicate an indirect or nonspecific cannabinoid effect. It is interesting that a similar dose of Δ^9–THC, 240 mg/kg/day, but in oil and given by gavage to A/J mice during days 11 and 12 or 12 and 13 of gestation, and controlled for food deprivation on day 12, did not change the incidence of resorption (Bloch *et al.*, 1979). This difference in activity may be a reflection of a lower blood cannabinoid concentration because of the oil vehicle and of gastric metabolism.

Fournier *et al.* (1976), having available a reference population of 1,850 births with 14,430 rabbit fetuses, found that ingestion of CME (at a dose that delivered 30 mg Δ^9–THC/kg/day) by 40 pregnant rabbits during days 5–12 of pregnancy resulted in increases in the resorption rate (the rate in the reference population was 5.1%; in the control group, 4.1%; and in the treated group, 10.0%), the percentage of macerated fetuses, 5.1%, 4.1%, and 8.3%, respectively, and of stillbirths, 4.2%, 4.4%, and 10.2% respectively. Subcutaneous Δ^9–THC and intragastric thalidomide (positive control) administration also were associated with a dose-related reduction in viable fetuses per rabbit litter (Sofia *et al.*, 1979). CME has been the predominant form in which cannabinoids have been administered to pregnant rabbits and, with one exception (Cozens *et al.*, 1979), it has resulted in smaller litter sizes.

Growth Retardation

Fetal or neonatal growth retardation and "stunting" were fre-

TABLE 7

Effects of Marihuana Derivatives on Pregnancy and Fetal Development in Laboratory Animals

Species	Strain	Cannabinoid	Dose (mg/kg/day)	Veh.	Duration (days of gestation)
Rat	N.S.	CME	0.2%	?	"months"
Rat	Inbred Albino	CME	4.2	1%T	1–6
Rat	Long-Evans	Δ^9–THC	0.01–200	O.o.	1–20
Rat	Wistar	Δ^8–,Δ^9–THC	20, 40(b)	O.o.	1–20
		Δ^9–THC	100–250	O.o.	9–16
Rat	Wistar	Δ^9–THC	10	O.o.	10–12
Rat	Wistar	Δ^9–THC	5, 20	P.G.	9–21
Rat	Wistar	Δ^9–THC	3.3	cig.	1–21
Rat	Charles River	CME	30–300	N.S.	6–15
		Δ^9–THC	5–50	N.S.	6–15

Abbreviations: VEH. = vehicle; N.S. = not stated; N.D. = not determined; *1%T* = 1% Tween 80 in saline; *10%T* = 10% Tween 80 in saline; *O.o.* = olive oil; *S.o.* = sesame oil; *P.G.* = propylene glycol; *ETOH* = anhydrous ethanol. Table reproduced from Bloch *et al.* (1978), with permission of publisher (Academic Press, Inc.).

(a) gross examination of external appearance only

(b) injected every other day for 30 days prior to conception plus every day until day 20 of gestation

(c) no effects were obtained when rats were subjected to same protocol beginning 14 (females) and 60 days (males) prior to mating and continued into pregnancy (14 or 21 days)

(d) effects of treatment *not* expressed quantitatively

(e) dose given for 2-day periods, i.e., 8–9, 10–11, and 12–13

Route of Adminis- tration	Litter Size	Effects on: Fetal Growth	Terato- genicity	Effective Dose/ Remarks	Reference
p.o.	reduced	?	none		Miras, 1962
i.p.	reduced	reduced	yes		Persaud and Ellington, 1968
s.c.	reduced	none	none(a)	100, 200 mg	Borgen *et al.*, 1971
s.c.	none	none	none		Pace *et al.*, 1971
s.c.	N.S.	reduced	none		
s.c.	N.S.	none	none		Borgen, 1973
p.o.	N.S.	N.S.	yes		Siegel *et al.*, 1977
smoke	N.S.	reduced	yes		Fried, 1976
p.o.	none	N.S.	none		Haley *et al.*, 1973
p.o.	none	N.S.	none		

(f) not teratogenic when administered on day 8, 10, or 16; little or no growth retardation on days 8, 10, or 12

(g) gave THC "...before and during gestation and lactation" (Maker *et al.*, 1974)

(h) males and females received 50 to 150 doses prior to mating; time between last dose and mating was from 48 to 535 days. Eight offspring from 3 females, including one fetal death

(i) statistically significant increase in bent tails at 100 mg/day, days 7–10, and in gyropodia at 500 mg on day 10. However, Joneja (1977) attaches little meaning to these findings.

(j) cleft palate incidence greater than vehicle control at $p = 0.1$

(k) found embryocidal effect during administration on day = 6–10, 6–13 and 6–15

TABLE 7 (CONTINUED)

Species	Strain	Cannabinoid	Dose (mg/kg/day)	Veh.	Duration (days of gestation)
Rat	Charles River	CME	3–30	N.S.	15–wean
		Δ^9–THC	0.5–5.0	N.S.	15–wean
Rat	Sprague-Dawley	Δ^9–THC	25–100	P.G.	6–15
Rat	Wistar	Δ^9–THC	30–120	?	10–12
Rat	Wistar	Δ^9–THC	30–120	ETOH	4
Rat	Fischer	Δ^9–THC	0.8–3.8	cig.	6–15
		Δ^9–THC	12.5–50	S.o.	6–15
Mouse	A/J	Δ^9–THC	120, 240	1%T	12–13
Mouse	N.S.	CME	16	1%T	1–6
		CME	16	1%T	6
Mouse	N.S.	Δ^9–THC	200	?	8–9
Mouse	Swiss-Webster	Δ^9–THC	200	10%T	8–13(e)
Mouse	Swiss-Webster	Δ^9–THC	40–100	10%T	6–15
Mouse	Swiss-Webster	Δ^9–THC	50, 200	10%T	8–13(e)
Mouse	Swiss-Webster	Δ^9–THC	25, 50, 75	10%T	8–10/12–14
		Δ^9–THC	300	10%T	12 or 14
Mouse	Swiss-Webster	Δ^9–THC	100–400	O.o.	7–11(1x)
	DBA/2J	Δ^9–THC	100–400	O.o.	7–11(1x)

Route of Administration	Effects on:			Effective Dose/ Remarks	Reference
	Litter Size	Fetal Growth	Teratogenicity		
p.o.	none	N.S.	none	(c)	Wright *et al.*, 1976
p.o.	reduced	N.S.	none	5 mg (c)	
s.c.	none	none	none		Banerjee *et al.*, 1975
s.c.	reduced	?	none		Uyeno, 1973
s.c.	reduced	N.S.	none		Uyeno, 1975
smoke	none	none	none		Rosenkrantz, 1979
p.o.	reduced	reduced	none		Rosenkrantz, 1979(k)
p.o.	reduced	N.S.	yes		Joneja, 1977
i.p.	complete	resorption	none	(d)	Persaud and Ellington, 1967
i.p.	reduced	reduced	none		
i.p.	reduced	?	none		Phillips, 1971
i.p.	reduced	reduced	N.D.	growth ↓: 10–13 days	Harbison and Mantilla-Plata, 1972
i.p.	reduced	reduced	yes	100 mg	Mantilla-Plata *et al.*, 1975
i.p.	reduced	reduced	yes	resorption max.: 8–9 days	Mantilla-Plata and Harbison, 1976b
i.p.	reduced	reduced	yes	*ter.*: 75 mg, days 12–14 (f)	Harbison *et al.*, 1977
i.p.	reduced	reduced	yes		
p.o.	none	reduced	yes	200, 400 mg; days 8, 9, 10	Joneja, 1976
p.o.	reduced	reduced	yes		

TABLE 7 (CONTINUED)

Species	Strain	Cannabinoid	Dose (mg/kg/day)	Veh.	Duration (days of gestation)
Mouse	CF1–S	Δ^9–THC	5	food	1–20
Mouse	Charles River CD–1	Δ^9–THC	5–150	S.o.	6–15
Mouse	Swiss-Webster	Δ^9–THC	0.8–3.8	cig.	6–15
	Charles River CD–1	Δ^9–THC	12.5–50	S.o.	6–15
	Charles River CD–1	Δ^9–THC	150–600	S.o.	6–15
Mouse	A/J	Δ^9–THC	60–240	S.o.	11,12; 12,13
Rabbit	New Zealand	CME	130–500	oil	7–10
Rabbit	New Zealand White	CME	3–90	N.S.	6–18
		Δ^9–THC	0.5–15	N.S.	6–18
Rabbit	Fauve de Bourgogne	CME	15, 30	tablet	5–12
Rabbit	New Zealand White	Δ^9–THC, CME	0.5–15	pill	6–18
Rabbit	New Zealand White	CME	30, 150	S.o.	6–18
Rabbit	New Zealand White	Δ^9–THC	15–60	P.G.	7–19

Route of Administration	Litter Size	Effects on: Fetal Growth	Teratogenicity	Effective Dose/ Remarks	Reference
p.o.	none	none	N.D.	(g)	Maker *et al.*, 1974
p.o.	none	none	none	(Skeletal malformations?)	Fleischman *et al.*, 1975
smoke	reduced	none	none		Rosenkrantz, 1979
p.o.	reduced	reduced	none		
p.o.	reduced	reduced	none		
p.o.	none	none	?	(j)	Bloch *et al.*, 1979(g)
s.c.	reduced	reduced	?	250, 500 mg; edema	Geber and Schramm, 1969b
p.o.	reduced	N.S.	none	90 mg	Haley *et al.*, 1973
p.o.	none	N.S.	none		
p.o.	reduced	reduced	yes	few abnormals	Fournier *et al.*, 1976
p.o.	none	none	none		Wright *et al.*, 1976
?	none	reduced	none		Cozens *et al.*, 1979
s.c.	reduced	reduced	none		Sofia *et al.*, 1979

TABLE 7 (CONTINUED)

Species	Strain	Cannabinoid	Dose (mg/kg/day)	Veh.	Duration (days of gestation)
Hamster	Golden	CME	25–300	oil	6–8
Hamster	Golden	CME	200, 300	O.o	6–8
Hamster	Golden	Δ^9–THC	125–500	O.o.	7–12(1x)
		Δ^9–THC	25–100	O.o.	7–12
Chimpanzee		Δ^9–THC	1.0–2.1	N.S.	(h)
Monkey	Rhesus	Δ^9–THC	2.4	food	365

quently reported after the administration of larger amounts of CME or Δ^9–THC to mice, rats, rabbits, and hamsters (review in Bloch *et al.*, 1978; Sofia *et al.*, 1979). In general, schedules of administration which led to increased resorption also resulted in growth retardation in the surviving fetuses or neonates. In studies with mice, rabbits, and hamsters, when the pertinent results were given, this relationship always existed (Table 7). Growth retardation here was the product of drug administration during the embryonic and organogenic phases, rather than the fetal phase of development.

In one of the few studies in which CME composition was determined (doses per day were 3 mg/kg Δ^9–THC, 15 mg/kg CBN, 2.5 mg/kg cannabichromene, and 2.5 mg/kg CBD), administration of the extract over days 6–18 of rabbit pregnancy diminished litter weight by 31% (Cozens *et al.*, 1979). Fried and Charlebois (1979a) demonstrated a 9% smaller birth weight among Wistar rats whose mothers had inhaled cannabis smoke (16 mg Δ^9–THC/kg) during 19 days of gestation. The cannabis effect was magnified by cross-fostering pups to cannabis-inhaling mothers during lactation but attenuated or eliminated if the mothers were treated during the 19-day premating period. In a second paper,

Route of Administration	Effects on:			Effective Dose/ Remarks	Reference
	Litter Size	Fetal Growth	Teratogenicity		
s.c.	none	reduced	yes	200, 300 mg; edema	Geber and Schramm, 1969a
s.c.	N.S.	none	none		Pace *et al.*, 1971
p.o.	reduced	reduced	(i)		Joneja, 1977
p.o.	reduced	reduced	(i)		
p.o.	—	none	none		Grilly *et al.*, 1974
p.o.	2 births	reduced	—	1 with hydrocephalia	Sassenrath and Chapman, 1975

Fried and Charlebois (1979b) reported a reduction in the adult weights of the F_2 offspring of rats exposed prenatally to marihuana smoke (see this section: Functional Maldevelopment). In studies involving marihuana smoke inhalation and exposure, possible synergistic effects of cannabinoids, CO, and other volatile products of cigarette pyrolysis must be kept in mind.

Teratogenic Effects

Large doses of Δ^9-THC, i.e., amounts exceeding 100 mg Δ^9-THC/kg body weight/day and aggregate intake of at least 200 mg per treatment regime, administered during specified stages of development to pregnant mice or hamsters are associated with an increased incidence of structural malformations. CME may be more of a teratogen than Δ^9-THC. Rats, unlike mice, are quite resistant to any structural teratogenic activity of cannabinoids or cannabis. A marihuana influence on primate or human development has not been detected. Nevertheless, effects of prenatal exposure may become apparent only in adult life, as shown in rats and mice (Fried and Charlebois, 1979b; Dalterio, 1980).

The initial observation suggesting marihuana to be teratogenic was that of Persaud and Ellington (1968). They reported congenital defects in *rat* fetuses of mothers given 4.2 mg marihuana resin i.p./kg/day on days 1–6 of gestation. In 93 fetuses from 13 experimental rats, 57% were malformed as compared to no malformations in 49 fetuses from 7 control rats. Syndactyly (76% of affected fetuses), encephalocele (57%), phocomelia (15%), and eventration of abdominal viscera (30%) were the most common malformations. Striking as these results are, they still await confirmation. None of the subsequent studies used i.p. administration in rats, and only one administered CME (Wright *et al.*, 1976) as distinct from Δ^9–THC.

One additional publication reported data interpreted as showing teratogenic effects, namely asymmetry in the mandibular dentition of offspring from rats given oral Δ^9–THC, 5 or 20 mg/kg (Siegel *et al.*, 1977); no dose-response relationship existed. All other studies did not demonstrate teratogenic activity of CME or Δ^9–THC in rats (Borgen *et al.*, 1971; Pace *et al.*, 1971; Haley *et al.*, 1973; Banerjee *et al.*, 1975; Uyeno, 1975; Wright *et al.*, 1976; Rosenkrantz and Hayden, 1979). (The last was the only attempt to relate circulating Δ^9–THC levels to biological effect.)

Exposure to large quantities of Δ^9–THC seems to induce malformations in mice and hamsters. A single i.p. injection of 300 mg Δ^9–THC into 12- or 14-day pregnant Swiss-Webster *mice* led to fetuses with respective 50% and 27% frequency of cleft palate; 100 mg/kg/day during days 6–15 of gestation gave an 11% incidence (Mantilla-Plata *et al.*, 1975). Treatment with lesser amounts or earlier or later in gestation, was essentially without effect. The incidence of cleft palate was greatly increased by pretreatment with SKF-525A or phenobarbital (Harbison *et al.*, 1977). SKF-525A may facilitate Δ^9–THC transfer to the fetus by inhibiting maternal metabolism and thus raising circulating levels, while phenobarbital may induce fetal metabolism of Δ^9–THC to an active metabolite (Harbison *et al.*, 1977).

Joneja (1976) also reported structural abnormalities in Swiss-Webster and DBA/AJ mice, given a single dose of Δ^9–THC (200 or 400 mg/kg) intragastrically on gestational day 8, 9, or 10. The malformations consisted of exencephaly and, of less certain significance, fused ribs and cleft palate. Joneja's extensive study employed adequate numbers of mice. However, a clear dose-response pattern for the frequency of malformations was not found. The frequency of other soft-tissue or skeletal abnormalities did not exceed control values; administration of lower doses, by other routes or on days 7 or 11, was ineffective.

Groups of 10 A/J mice given Δ^9–THC at doses of up to 240 mg/kg/day intragastrically on days 12–13 of pregnancy tended ($P < 0.1$) to show a dose-dependent increase in incidence of cleft palate formation (Bloch *et al.*, 1979). This was not found in mice treated on days 11–12. No malformations were noted in fetuses from mouse mothers subjected to oral Δ^9–THC treatment of up to 600 mg/kg/day on days 6–15 (Fleischman *et al.*, 1975; Rosenkrantz and Hayden, 1979) or up to 100 mg/kg/day on days 7–11 (Joneja, 1976, 1977b).

CME administered in s.c. doses of 100 to 300 mg/kg/day to *hamsters* on days 6, 7, and 8 of pregnancy produced fetal congenital defects and edema (Geber and Schramm, 1969a). Malformations consisted of phocomelia, omphalocele, spina bifida, exencephaly, myelocele, and multiple malformations (no data on frequency were provided). Source of marihuana and an environmental variable influenced the frequency of defects and edema; both indices differed depending on the use of New Jersey (rich in cannabis-seed oil) or Mexican CME, and the time of year the studies were carried out. Up to 500 mg/kg/day Δ^9–THC, administered by gavage during gestational days 7–12, produced only a small increase in the incidence of external anomalies and none in internal anomalies (Joneja, 1977a).

Geber and Schramm (1969b) repeated their work using *rabbits*. A 5%–35% incidence of malformation and edema was seen when 250 or 500 mg/kg CME was given daily on gestation days 7 through 10. The groups were statistically of adequate size and none of 48 to 100 fetuses in the control groups showed abnormalities or edema. Fournier *et al.* (1976) claimed a teratological effect of CME administered orally to rabbits during days 5–12 of pregnancy (see Table 7). The very low incidence of total malformation found (0/68, 1/74 in the control groups; 1/60, 1/49, 3/60, 4/73 in the experimental groups) requires confirmation and extension before the significance of these data can be evaluated. Haley *et al.* (1973), giving Δ^9–THC or CME orally for 13 days during pregnancy (days 6–18), found no evidence of maldevelopment in 794 30-day-old rabbit fetuses. Similarly, Cozens *et al.* (1979) administering CME (at a daily dose that delivered 3 mg/kg Δ^9–THC, 15 mg/kg CBN, 2.5 mg/kg CBD, and 2.5 mg/kg cannabichromene) and Sofia *et al.* (1979) injecting 15–60 mg/kg Δ^9–THC s.c. during days 6–19 of gestation, did not detect teratogenesis.

Two reports deal with primates. Two macaque females, receiving 2.4 mg/kg Δ^9–THC p.o. for 1 yr, gave birth to 2 babies; one was a hyperactive but otherwise normal male, the other a hydrocephalic female who died shortly after birth (Sassenrath and Chapman, 1975). Eight offspring from chimpanzees who had smoked Δ^9–THC prior to mating were normal (Grilly *et al.*, 1974).

Functional Maldevelopment

Recent experimental studies have drawn attention to adult reproductive and endocrine consequences of exposure to cannabinoids during embryonic differentiation and fetal development.

Fried (1976) exposed 5 pregnant rats to marihuana smoke and 4 pregnant rats to cannabinoid-free marihuana placebo smoke, once daily for 9 min during days 1–19 of gestation. Litters were cross-fostered. The offspring of the experimental mothers had lower birth weights and retarded eye-opening and incisor eruption. These deficiencies were accentuated when pups were cross-fostered by rats exposed during lactation to marihuana smoke. Extending the period of marihuana smoke inhalation to a 19-day period prior to gestation (Fried and Charlebois, 1979a) tended to attenuate these effects of gestational cannabinoid exposure. In further work, Fried and Charlebois (1979b) examined the reproductive and teratogenic consequences in the F_1 and F_2 offspring of the marihuana-exposed rats used in the Fried (1976) study. The F_1 offspring, 6 mo old and having also received 15 i.p. doses of 8 mg/kg Δ^9–THC (!) during the 4th month of age, were less fertile, showed longer latency to sperm plug appearance, and had decreased seminal vesicle, prostate and ovarian weights compared with the F_1 offspring of the placebo-exposed controls. The F_2 offspring had reduced body weights, and delayed incisor eruption and eye-opening, suggesting that marihuana inhalation by the original group had exerted at least in part a genetic effect. A larger study is required to place these interesting results on a firmer statistical basis and to separate the effects of prenatal inhalation from those of postnatal injection.

The offspring of mice exposed orally to 50 mg/kg Δ^9–THC/day from one day before parturition through 6 days postpartum, had decreased testis weight and increased serum LH concentrations during prepubertal (35–37 days) and adult (60–80 days) periods, and increased body weight as adults (Dalterio, 1980). Serum FSH levels were unaffected, and seminal vesicle weights were slightly reduced in the adult animals. No effects were discernible at weaning (21 days). CBN administration diminished prepubertal serum testosterone and LH levels.

Summary

In mice, rats, rabbits, and hamsters, marihuana extracts and Δ^9–THC, in sufficient dosage, produce resorption, growth retardation, or malformations. Their lethal action is perhaps more pronounced during the embryonic stages of development although this requires more study. The locus (or loci) of action of marihuana resulting in resorption is unknown.

In the studies with mice by Mantilla-Plata *et al.* (1975), Harbison *et al.* (1977), and Joneja (1976), a teratogenic response was clearly observed:

(i) the frequency of two specific developmental lesions, cleft palate and exencephaly, was quite high and showed an indistinct relationship to dose;

(ii) the susceptible period for the induction of cleft palate and exencephaly coincided with the critical period of palate and brain development (Wilson, 1965; Burdi *et al.*, 1972), and that found after the administration of other teratogens (Fraser and Fainstat, 1951; Wilson, 1965; Burdi *et al.*, 1972; Saxén, 1976);

(iii) agents which affected Δ^9-THC metabolism enhanced its activity in interfering with palate closure (Mantilla-Plata and Harbison, 1976a; Harbison *et al.*, 1977), and

(iv) sufficient control and experimental groups with enough litters per group were used (Palmer, 1972).

In five other studies with rats (Persaud and Ellington, 1968), mice (Bloch *et al.*, 1979), hamsters (Geber and Schramm, 1969a; Joneja, 1977a) and rabbits (Geber and Schramm, 1969b), treatment probably caused the observed malformations although the results or experimental design prevent a definite judgment.

It should be noted that generally several hundred milligrams of CME or Δ^9-THC per kg body weight were required to elicit a teratogenic response in mice, rabbits, and hamsters. How much of these large doses reaches the fetus? In mice, perhaps 0.1%, or 10 μg per fetus, based on the Harbison and Mantilla-Plata (1972) placental transfer studies in which 0.1 nCi of an injected maternal dose of 0.2 μCi/10 g body weight was present in 100 mg fetal homogenate 4 hr after injection. This estimate assumes 25 g maternal weight, 0.5 g fetal weight (day 15 of gestation) and i.p. injection in saline. Similarly in rabbits, 0.1% placental transfer would result in 1 mg Δ^9-THC reaching each fetus. These speculative estimates ignore the role of route of administration, gestational age, metabolism, species placental differences, etc., in determining how much of the administered dose reaches the fetus. However, these estimated values suggest an embryonic-fetal sensitivity to Δ^9-THC that is at least equal to that found in adults.

The data also illustrate the difference between CME and Δ^9-THC. Except in mice, teratogenic effects tended to be seen more often after CME administration than after purified Δ^9-THC intake. This difference calls attention to the role of other cannabinoids and of noncannabinoids in the effects of marihuana.

Growth retardation, as manifested in reduced fetal or neonatal weight, was frequently observed. A clear-cut maldevelopmental effect was seen less often. Whether growth retardation and teratogenicity are a direct consequence of cannabinoid administration or a result of diminished food consumption remains to be resolved. Δ^9–THC diminished food intake in rats (Manning *et al.*, 1971; Pace *et al.*, 1971; Banerjee *et al.*, 1975; Drewnowski and Grinker, 1978) and rabbits (Banerjee *et al.*, 1976) and may interfere with gastrointestinal absorption (Joneja, 1976). Reduced food consumption (Kalter, 1965) or starvation (Runner, 1959) has been shown to be teratogenic in mice. The incidence of cleft palate rose from 1.4% to 5.6% when food intake was restricted to 40% of normal during the 12th through 16th day of gestation (Kalter, 1965). In the studies by Mantilla-Plata *et al.* (1975) the high incidence of cleft palate occurring after treatment with 300 mg Δ^9–THC was associated with a significant decrease in fetal weight gain.

7. CHROMOSOMAL ABERRATIONS

During the past 11 yr, about two dozen publications on the possible cytogenetic effects of cannabinoids have appeared (Table 8). Two-thirds of these studies have dealt with examination in human chromosomes, and the remainder with rodent chromosomes.

Cytogenetic analyses of lymphocyte cultures from chronic marihuana smokers have provided contradictory results. Stenchever *et al.* (1974) reported a tripling of cells with chromosomal breaks (3.4% vs 1.2%), and Morishima *et al.* (1976a) observed an increased incidence of lymphocytes with hypoploidy, i.e., metaphase nuclei with less than 30 chromosomes. Herha and Obe (1974) and Kumar and Kunwar (1971) reported increased chromosomal abnormalities in chronic marihuana smokers; the statistical treatment of their data has been questioned (U.S. Secretary of Health, Education and Welfare, 1976). In contrast, the results of other studies revealed no chromosomal abnormalities (Dorrance *et al.*, 1970; Gilmour *et al.*, 1971; Martin *et al.*, 1974). No clear association between chromosome response and duration and intensity of cannabis intake emerged from these studies.

In four controlled, prospective studies, in which experienced smokers adhered to a regimen of marihuana consumption varying from 1 to 15 cigarettes per day for 5 to 13 days, no change in the incidence of chromosomal breaks and gaps was observed (Nichols *et al.*, 1974; Matsuyama *et al.*, 1976, 1977; Morishima *et al.*, 1979). In the heavy smoking group (12–15 cigarettes/day for one month) of Morishima *et al.* (1979), a significant increase in lymphocytes with hypoploidy was noted (from 10%–16% before smoking to 30%–43% during smoking). Cells returned to a euploid chromosome complement with abstinence from

TABLE 8

Chromosomes in Cells from Marihuana and Cannabinoid-Exposed Humans and Rodents

Cannabinoid Exposure	Sample size		Reference
1. *Higher incidence* of abnormalities in chromosomes of cultured *human lymphocytes:*			
<1–>2 cig/wk	C = 20,	E = 49	Stenchever *et al.*, 1974
3–10 cig/wk	C = 10,	E = 5	Morishima *et al.*, 1976
12–15 cig/day for 29 days	C = 7,	E = 5	Morishima *et al.*, 1979
27 μg olivetol/ml *in vitro*	—	—	Morishima *et al.*, 1976
2. *No significant effect* on chromosomes of cultured *human lymphocytes*:			
≥20 cig/wk	C = 15,	E = 18	Martin *et al.*, 1974

Chromosomal abnormalities consisted of breaks and gaps (Stenchever *et al.*, 1974; Leuchtenberger and Leuchtenberger, 1976) or aneuploidy (micronuclei) (Morishima *et al.*, 1976, 1979).

C = nonsmokers or abstaining smokers; E = smokers; wk = week(s); cig. = cigarette(s)

(a) marihuana containing 2.2% Δ^9–THC. Smoker group (E = 13) served as its own control group (presmoke)

(b) Δ^9–THC content of 1% (7 smokers) or 2% (7 smokers)

(c) CME (= 20 mg Δ^9–THC, no other cannabinoids), hashish (mixture of cannabinoids), or pure Δ^9–THC administered for 5 days, once per day. Control subjects received cannabinoid on days 1 and 5 only. N = 8 or 10 CME, 2 hashish, 1 Δ^9–THC subject each for control and experimental. A *second* series, N = 3, Δ^9–THC only, 12-day administration

TABLE 8 (CONTINUED)

Cannabinoid Exposure	Sample size		Reference
1–7 cig/wk	C = 10,	E = 5	Dorrance *et al.*, 1970
2–3 cig/wk	C = 10,	E = 5	Morishima *et al.*, 1976
<0.5 cig/wk	C = 16,	E = 13	Gilmour *et al.*, 1971
4–10 cig/day for 63 + 8 days	E = 13(a)		Matsuyama *et al.*, 1976
1 cig/day for 28 days	C = 7,	E = 14(b,c)	Matsuyama *et al.*, 1977
CME, hashish, Δ^9–THC		(c)	Nichols *et al.*, 1974
0.1–10 μg Δ^9–THC/ml *in vitro*	—	—	Morishima *et al.*, 1976; Stenchever *et al.*, 1972
30, 50 μg Δ^8–THC/ml *in vitro*	—	—	Neu *et al.*, 1970
80–150 μg CME resin/ml *in vitro*	—	—	Martin *et al.*, 1974
3. Effects on chromosomes of other cultured *human* cells:			
Lung: Δ^9–THC smoke *in vitro:*	*Effect* ±		Leuchtenberger and Leuchtenberger, 1976
Skin: Δ^9–THC ± S9 fraction	*No* effect		Zimmerman *et al.*, 1978

TABLE 8 (CONTINUED)

Cannabinoid Exposure	Reference
4. *Significant* effects on rodent cells:	
a. Abnormal morphology of *spermatozoa* of *mice* injected i.p. with 5–25 mg Δ^9–THC or CBN/kg/day for 5 days	Zimmerman *et al.*, 1979
b. Increased DNA in cultured *mouse lung* cells exposed to 0.4% or 4% Δ^9–THC–marihuana smoke for 5 days	Leuchtenberger and Leuchtenberger, 1976
5. *No significant* effects on chromosomes of *rodent* cells in various systems:	
Bone marrow cells (mice): 5–20 mg Δ^9–THC/kg/day for 7 days i.p.	Van Went, 1978
Bone marrow cells (mice): 10–200 mg/Δ^9–THC/kg day for 5 days p.o.	Legator *et al.*, 1976
Bone marrow cells (hamsters): 10, 1,000 mg Δ^9–THC/kg/day once s.c.	Joneja and Kaiserman, 1978
Embryo cell culture (rat): 4.2 mg resin/day, days 1–6 Lymphocyte culture (rat): pregnancy	Martin *et al.*, 1974
Dominant Lethal test (mice): 10–200 mg Δ^9–THC/kg/day for 4 wk p.o.	Legator *et al.*, 1976

smoking, and there was no evidence of increased anaphase or telophase bridge formation.

Lung fibroblasts in cultures exposed to marihuana smoke *in vitro* also tended towards reduced chromosome complements (Leuchtenberger *et al.*, 1976). In general, leukocytes kept in cultures containing marihuana resin (Martin, 1969; Martin *et al.*, 1974), Δ^8–THC (Neu *et al.*, 1970) or Δ^9–THC (Stenchever and Allen, 1972) showed no change from control cultures in the incidence of chromosome breaks, gaps, or exchanges. Lymphocytes cultured in a medium containing olivetol, a compound sharing structural similarity with cannabinoids, at 50–150 μM concentrations, showed an increased frequency of hypoploidy, abnormal chromosome segregation, and mitotic behavior (Morishima *et al.*, 1976a and b). The concentrations of olivetol seem high; lower amounts of Δ^9–THC (6.4 μM) were innocuous. In a study with human skin fibroblasts (Zimmerman *et al.*, 1978), the incidence of chromosomal breaks plus gaps or sister chromatid exchanges in fibroblasts cultured with Δ^9–THC or Δ^9–THC activated by preincubation with liver S9 microsomal fraction (i.e., Δ^9–THC and its metabolites) did not exceed that of control cultures. By comparison, S9-activated aflatoxin increased the incidence of these abnormalities 10–30-fold.

Diverse studies of chromosomal replication in rodent cells indicate little interference by cannabinoids. Bone marrow cells from mice (Legator *et al.*, 1976; Van Went, 1978) and hamsters (Joneja and Kaiserman, 1978), and cultures of rat embryonic cells or adult leukocytes (Martin *et al.*, 1974), exposed to Δ^9–THC or CME exhibited a normal frequency of chromosomal changes and hypoploidy. A decrease in mitotic index has been reported in several studies (Neu *et al.*, 1970; Stenchever and Allen, 1972; Martin *et al.*, 1974; Joneja and Kaiserman, 1978). Leuchtenberger *et al.* (1976) reported increased rates of mitosis and polyploidy in cultures of murine lung fibroblasts exposed to marihuana smoke.

The cannabinoids Δ^9–THC and 8α, 9α–epoxyhexahydrocannabinol were not mutagenic in direct assays with *Salmonella typhimurium*, either in the presence or absence of liver S9 microsomal fraction (Legator *et al.*, 1976; Zimmerman *et al.*, 1978; Glatt *et al.*, 1979). In contrast, condensates of marihuana smoke, similar to those of tobacco smoke, were found to have mutagenic activity against the *Salmonella typhimurium* strain TA 98 after metabolic activation with S9 microsomal fraction (Busch *et al.*, 1979; Wehner *et al.*, 1980).

In conclusion, *in vivo* and *in vitro* exposure to purified cannabinoids or cannabis resin failed to increase the frequency of chromosomal damage or of mutagenesis; the abnormal morphology of sperm seen after Δ^9–THC or CBN administration to a strain of mice (see Section 2: Spermatogenesis) (Zimmerman *et al.*, 1979) may represent an exception. In contrast to purified cannabinoids, marihuana smoke exposure has been reported to be associated with chromosomal aberrations (but there are also negative reports, hypoploidy, mutagenicity in the Ames test, and (Fried and Charlebois, 1979b) impaired development in the F_2 generation of a mouse strain (see Section 6: Functional Maldevelopment). Studies to date have not shown cytogenetic or mutagenic effects which are definitely attributable to cannabinoids, unique to *Cannabis sativa*, or unambiguously identifiable in the human population. The possible effects of marihuana merit further studies to

(i) delineate the chromosomal and genetic effects,

(ii) determine the loci of action, and especially,

(iii) to identify any active compounds unique to *Cannabis sativa.*

8. CONCLUSIONS AND SUMMARY

Endocrine and Reproductive Systems

Endocrine studies have concentrated on the activities of the male and female reproductive endocrine system and on the adrenal cortex-brain axis. A few isolated reports deal with thyroid function, growth hormone release, and insulin secretion in response to cannabinoid exposure.

The following conclusions are drawn from rodent studies:

(i) Cannabinoids disrupt normal *male reproductive* physiology. Testicular metabolic activity and *in vitro* testosterone synthesis are decreased; plasma testosterone and LH levels fall and, upon chronic intake, androgenic target tissues show varying degrees of functional and morphological involution. Prolonged cannabinoid intake leads to diminished spermatogenesis. The effects of marihuana and cannabinoids on male reproductive endocrinology and on spermatogenesis are reversible and no permanent changes have been described following cessation of cannabinoid intake.

(ii) The acute or single administration of Δ^9–THC to *nonpregnant* females transiently inhibits functioning of the hypothalamic-pituitary-gonadal axis, as in the male. Plasma LH and prolactin levels are decreased; the preovulatory LH surge is suppressed, and estrus is delayed. Chronic Δ^9–THC or CME intake seems to impair reproductive function reversibly. Uteri and vagina show signs of morphological and functional involution, and ovarian function may be affected. Estrous cycles are inconsistently interrupted or abolished.

In *pregnant* females, Δ^9–THC exerts few maternal effects unique to pregnancy. High doses suppress or diminish the maternal weight gain of pregnancy. Δ^9–THC decreases prolactin levels, which may explain the reduced and inadequate *lactation* seen in the postpartum, cannabinoid-ingesting rat. Ingested Δ^9–THC appears in mammary tissue and milk and is transferred to suckling pups.

(iii) Cannabinoids and CME stimulate *adrenal cortical* function. Acute administration results in increased plasma corticosterone concentrations; long-term and short-term exposure leads to adrenal weight increase and thymus weight decrease.

(iv) *Thyroid* function is diminished by cannabinoids.

The few studies on *monkeys* and other *nonhuman primates* tend to confirm a suppressive effect of cannabinoids on pituitary gonadotrophin release, and on the blocking of ovulation. Δ^9–THC is found in maternal milk. Too few studies evaluating other parameters have been carried out to permit even tentative inferences.

Δ^9–THC, 11-OH-Δ^9–THC and *CBN* are active constituents of *Cannabis sativa.* The response of different systems to *CBD* seems to be more circumscribed and variable.

A primary *locus* of cannabinoid action is in the brain, including probably the hypothalamus. Cannabinoid stimulation of the adrenal cortex can be abolished by agents and procedures which block pituitary ACTH production, while LH-RH will stimulate pituitary LH release in the Δ^9–THC-blocked rat.

CME and Δ^9–THC probably also exert a direct inhibitory effect on gonadal and adrenal cortical function. This is especially true for the testes, in which *in vivo* and *in vitro* experiments have demonstrated an inhibition of testosterone synthesis, perhaps via reduced cholesterol esterase activity or prostaglandin synthesis, the latter being involved in mediating trophic hormone effects. Diminished metabolic activity and macromolecule synthesis in testes following exposure to cannabinoids may explain the reduced spermatogenesis observed after cannabis intake.

Repeated cannabinoid administration may exert a direct effect on the uterus, and possibly also on prostate and mammary gland tissue. Interpretation of data is made difficult by differences in the effects of CME vs Δ^9–THC, the dosage required to produce an effect, and dose-response relationships. If direct effects exist, they require larger CME doses and may reflect a more general toxicity.

Δ^9–THC *concentrates* in tissues rich in lipid components, i.e., adipose tissue, corpus luteum, adrenal cortex, and mammary gland tissue. Other tissues do not seem to localize Δ^9–THC (or metabolites) preferentially. This may speak against the involvement of high-affinity, specific receptors in the mechanism of cannabinoid action. A membrane action has been suggested, involving perturbation of the lipid phase of membrane structures by increasing the fluidity and mobility of membrane components. The molecular mechanism of cannabinoid action remains to be elucidated. It must also be remembered that marihuana contains other components, which may have activity with quite different loci of action.

Development and Chromosomes

Radiolabeled Δ^9–THC administered to pregnant rodents results in a concentration gradient of mother > placenta > fetus. Placental uptake of radioactivity exceeds that of the fetus, with only slow release. This makes the placenta potentially a barrier against, but also a reservoir for, cannabinoid transfer into the fetus.

Cannabinoid administration during the first two-thirds of gestation is associated with increased resorption frequency and decreased birth weights in mice, rats, rabbits, and hamsters.

The administration of large doses of Δ^9–THC to mice during the critical periods of palate and brain development, respectively, is correlated with increased frequency of cleft palate and exencephaly. Cannabinoid-exposed hamsters also had a greater incidence of malformations. Other reports of cannabinoid-induced malformations cannot be considered as definitive. CME may contain constituents other than Δ^9–THC which are teratogenic.

Suggestive evidence exists that the products of marihuana smoke can cause chromosomal damage in human cells and mutagenesis in several test systems. This activity does not seem to reside in pure cannabinoids; a unique contribution by constituents or pyrolysates of *Cannabis sativa* remains to be established.

Animal Studies: Comments

Perhaps the major deficiency in animal work has been the paucity of studies in which the biological response to *and* the disposition of the administered CME or individual cannabinoid have been determined in the same animal. Stability of the CME constituents and of Δ^9-THC during storage (Garrett and Tsau, 1974; Garrett *et al.*, 1978; Cozens *et al.*, 1979), routes of administration (Lemberger, 1976; Mantilla-Plata and Harbison, 1976), and frequency of administration are three variables which influence plasma cannabinoid levels. Individual cannabinoids are metabolized and cleared from blood at rates that are dependent on such factors as the compound, species, and age. Some of the reported differences in biological responsiveness may well reflect variations in nature, or concentration of the cannabinoids or the duration of their interaction with a target site. In addition, pharmacokinetic information would facilitate comparison with human data.

More dose-response relationships need to be demonstrated so that the actions of cannabinoids can be related more specifically to observed effects. *In vitro* studies also require more kinetic data, especially where *in vivo* and *in vitro* results are contradictory, as with the adrenal cortex. The recent emphasis on experiments designed to isolate sites of action should be fruitfully sustained.

Human Studies

In *humans*, marihuana acutely depresses the activity of the male pituitary-testicular axis. By extension from work with rodents and Rhesus monkeys, a similar inhibitory effect may exist in females. Sustained marihuana intake probably initiates and maintains oligospermia. Other endocrine or reproductive effects have yet to be shown. At a minimum, surveys and controlled studies should be carried out to investigate the effects of cannabis on the function and reactivity of endocrine glands (systems) through determination of specified plasma hormone levels.

It seems doubtful that CME or Δ^9-THC is *teratogenic* in humans. The few reports of teratogenicity in rodents and rabbits indicate that cannabinoids are, at most, weakly teratogenic in these species.

How well have animal studies served as models for the human situation? Where a particular endpoint or system reacts uniformly to cannabinoid exposure in several species of several classes, including monkeys, a qualitatively similar response in humans may be inferred. This uniformity seems to be the case for acute and short-term responses of the reproductive system, including lactation.

The dosages used in animal studies can be related to human marihuana intake as calculated by Rosenkrantz and coworkers (Rosenkrantz and Braude, 1974, 1976; Rosenkrantz *et al.*, 1975; Rosenkrantz, 1976, 1979), who based their conversions on the LD_{10}

values of anti-tumor agents (Freireich *et al.*, 1966), relative body-surface areas, LD_{50} values of Δ^9–THC administered by different routes, and the loss of Δ^9–THC during the smoking of cannabis. On the basis of their equivalent dosages, it appears that the majority of studies used Δ^9–THC doses approximating the daily smoking of several marihuana cigarettes by humans. As the Δ^9–THC content of street marihuana has risen to 4%–5% lately (U.S. Secretary of Health, Education and Welfare, 1980), the equivalence drops to the consumption of 0.5–1 daily cigarettes, a level of consumption comprising about 10% of the marihuana-smoking population. If the levels of consumption of active marihuana constituents continue to rise, then some of the "high-dose"-induced effects seen in animals may also become manifest in humans.

While the dose range used seems to approximate the aggregate daily intake of a moderate or heavy smoker, most animal studies have not simulated the frequency, route, or other variable factors that complicate human marihuana consumption. Δ^9–THC or CME administration by gavage or injection is not equivalent to inhaling the volatile and pyrolyzed products of burning cannabis, a plant which contains at least 421 compounds from 18 chemical classes (Turner *et al.*, 1980). Differences in biological and activity rhythms, in the metabolic interactions of cannabinoids with other consumed exogenous agents, and in nutritional status have not been carefully investigated.

It is hoped that with increasing use of monkeys, and as far as possible human material, more data applicable to man will be forthcoming. At the same time, rodent experimentation will continue to serve well for studies on the mechanisms and cellular sites of marihuana action.

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Acute Psychological Effects of Marihuana in Man, Including Acute Cognitive, Psychomotor, and Perceptual Effects on Driving

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1. ACUTE EFFECTS OF MARIHUANA ON COGNITIVE, PERCEPTUAL, AND PSYCHOMOTOR FUNCTIONS

Overview of Prospective (Experimental) and Retrospective (Field) Models of Clinical Research

Studies of marihuana dealing with short-term effects—psychological, neuropsychological, cognitive, perceptual, and psychomotor—have a common denominator, namely the acute effects on mental processes. Longer-term effects on mental processes focus on the chronic user, and one of the issues here is that of brain damage. Complementary to the studies on mental processes are those investigations which single out or deal also with effects of marihuana on personality, for example, short-term effects on lifestyle or longer-term effects characterized as the "amotivational syndrome." Intersecting with the studies on mental processes and personality are those that are specifically concerned with the effects of marihuana on driving and, more recently, flying.

A methodological problem which has often been overlooked in the discussion of marihuana effects is the differentiation between prospective experimental research which uses a random or quasi-experimental design (administering drugs to observe consequences) and retrospective field research which relies on a design of self-assignment (i.e., relating the subjects' self-reported drug administration to observed consequences). Specifically, in evaluating the acute effects of marihuana, the prospec-

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tive experimental model permits the administration of a drug of a known potency in a standardized manner, thus enabling control of the phenomenon being studied and generalization of findings. Research into the effects of marihuana based on the retrospective field method relies exclusively on the subjective statements of the subjects regarding drug use. Frequently this results in under-emphasis of the importance of cultural context, and often multi-drug use is ignored. As there is no control regarding drug intake, generalizations from these data may accordingly be limited. Some of the discrepant findings in the literature can probably be accounted for in terms of these different models of clinical research. For example, in evaluating the short-term acute effects of marihuana on neuropsychological processes, one should *a priori* expect discrepancies between the results of those studies that measured effects during the acute, intoxicated state (experimenter-created variation of the experimental method) and those which measured self-described effects in users (since there is already variation between subjects with respect to dose and cultural context in the field method). The issues of control are much more profound in long-term studies on the effects of marihuana; generalizations may in fact be unwarranted, particularly from those studies which ignore the cultural context of marihuana use.

The Acute Effects of Marihuana on Psychological Functions, 1933–1946

The earliest culturally relevant experimental marihuana research consists of three studies (Siler *et al.*, 1933; Mayor's Committee on Marihuana, 1944; Williams *et al.*, 1946). Of these, the Mayor's Committee on Marihuana (1944) remains to date the landmark study of the acute effects of marihuana on psychophysical, intellectual, and personality functions. The review to follow will include only the psychophysical and intellectual components.

The subjects consisted of 5 naive individuals (no previous contact with marihuana) who were paid for their services, and 72 inmates (65 males and 7 females) from the Department of Corrections of New York City of whom 48 gave a history of marihuana smoking. The marihuana used in the study was administered orally as a "concentrate" or was smoked in the form of cigarettes (but neither the dose administered nor the smoking procedure was specified). Psychophysical and other functions were monitored by testing static equilibrium, hand steadiness, speed of tapping, strength of grip, simple and complex hand and foot reaction time, musical aptitude, auditory acuity, perception of time, and perception of length. The effect of marihuana on the psychomotor functions was found to depend primarily on the complexity of the function tested. More specifically: (i) simpler functions such as speed of tapping and simple reaction time were affected only slightly by large doses (5 ml of "concentrate") and negligibly, if at all, by smaller doses (2 ml); (ii) the more complex functions, including static equilibrium, hand steadiness, and complex reaction time, were unequivocally adversely affected by the administration of both large and small doses of marihuana. Intellectual functions were assessed by means of a battery including the following tests: Bellevue Adult Intelligence Test (BAIS); Army Alpha; Pyle's Digit Symbol; Cancellation Test; Form Board Test; Koh's Block Design Test; and Memory Tests. Marihuana was found to have a transitory adverse effect on mental functioning. More specifically: (i) the extent of intellectual impairment, the time of its onset, and its duration were all dose-related; (ii) the degree of intellectual impairment varied with the function tested, and more complex functions were more severely affected. In summary: (i) there was dose-related impairment with respect to static equilibrium, hand steadiness, and complex reaction time; (ii) there was a decrement in overall mental functioning and more particularly in memory, ability to handle number concepts, and problem-solving ability; and (iii) there were no significant changes in hand strength, auditory acuity, perception of length of lines, simple reaction time, or tapping speed.

The first published study that can withstand critical evaluation is that of Weil *et al.* (1968) who measured attention, general alertness, and muscular coordination in 17 subjects (9 naive and 8 experienced) under low dose (4.5 mg Δ^9–THC), high dose (18 mg Δ^9–THC), and placebo conditions, using a standardized smoking technique throughout. Sustained attention was not affected; general alertness and muscular coordination and attention decreased at both dose levels, but only for the naive subjects. Subsequent to the study of Weil *et al.* (1968), several investigators between 1969 and 1973 have reported on the psychological effects of smoked marihuana and these are summarized below.

Caldwell *et al.* (1969) failed to find changes in either visual or auditory threshold following the smoking of 3.9 mg Δ^9–THC by 12 experienced subjects, using a semistandardized smoking procedure. In a second study by Caldwell *et al.* (1970), it was found that marihuana minimally affected sensory acuity in a group of 20 subjects who smoked in an unstandardized manner until they felt "high" (the mean dose was 6.3 mg Δ^9–THC). Control groups were included in both studies.

Manno *et al.* (1970) measured motor performance and "mental performance in a condition of self-induced anxiety" under conditions of delayed auditory feedback in 12 experienced subjects. Subjects received placebo and two doses of marihuana (2.5 and 5 mg Δ^9–THC) in cigarette form administered in an unspecified manner, with no prior ingestion of alcohol or in combination with enough alcohol to achieve a blood level of 0.05% (50 mg/100 ml). Although marihuana impaired performance, no dose-response phenomenon was demonstrated. The alcohol and marihuana exerted additive effects in the impairment of motor performance.

Abel (1970, 1971a, b, c) measured memory during marihuana and control conditions in experienced subjects (groups varied in number from 8 to 26 subjects), but the marihuana was of unknown potency and was smoked according to unspecified procedures. He reported that marihuana did not affect retrieval of information already present in memory, but did interfere with the initial learning (significantly affecting acquisition processes involved in the storage of information). The author suggested that an inability to concentrate may be the explanation for marihuana-induced memory impairment; because of impaired concentration, rehearsal did not occur and information was not transferred to permanent memory.

Kiplinger and Manno (1971) and Kiplinger *et al.* (1971) measured motor and mental performance under conditions of delayed auditory feedback, and stability of stance in 15 subjects (7 naive and 8 experienced), measuring from 4 to 9 variables for each type of performance. Cigarettes containing 5 mg Δ^9–THC, three much lower dose levels, and a placebo were administered in an unspecified manner. Dose-dependent decrements were observed in 14 of the 19 measured variables.

Meyer *et al.* (1971) measured field dependence, attention, general alertness, time perception, task focusing, and muscular coordination in 12 subjects (6 "heavy"—i.e., daily—and 6 casual marihuana users). Experimental conditions were placebo, 2.3 mg Δ^9–THC, and a self-selected amount of marihuana (average dose of casual users was 3.8 mg Δ^9–THC, of heavy users 3.4 mg Δ^9–THC). The smoking procedure was unspecified. Whereas no statistical analyses of data were made, the authors stated that most of the perceptual tests showed a mild degree of impairment, the impairment being more evident in the casual smokers.

Dornbush *et al.* (1971) and Dornbush and Freedman (1972) studied short-term memory, reaction time, and time estimation in 10 experienced subjects. Cigarettes contained two dose levels of Δ^9-THC, low (7.5 mg Δ^9–THC) or high (22.5 mg Δ^9–THC), and placebo. The manner of smoking was unspecified. Short-term memory and reaction time were adversely affected only by the high dose of marihuana.

The Commission of Inquiry into the Non-Medical Use of Drugs (Le Dain, 1972) measured short-term serial position memory and general alertness (digit symbol substitution), among other variables, in subjects who smoked average doses of 0.7, 1.5, and 6.2 mg Δ^9–THC, using a standardized and closely controlled smoking technique. Impairment was found in the former but not the latter measure.

Other investigators who used higher dose levels reported detrimental effects on new learning (Rickles *et al.*, 1973, administered 14 mg Δ^9–THC and placebo) and attention (Galanter *et al.*, 1973, administered 10 mg natural Δ^9–THC, 10 mg synthetic Δ^9-THC, and placebo).

Several studies between 1968 and 1973 have reported the psychological effects of orally administered marihuana and these are summarized below. Clark and Nakashima (1968) and Clark *et al.* (1970) measured mirror tracing, depth perception, reaction time, time estimation, and learning in 12 and subsequently 18 naive subjects. Their dose of ethanolic extract of marihuana contained 20–50 mg Δ^9–THC. Learning, time estimation, and reaction time were most consistently affected by the drug.

Hollister and Gillespie (1970) measured muscular coordination and attention, general alertness, reaction time, muscular facility, flexibility of closure (i.e., ability to retrace in a field of dots a figure drawn in a similar field, with the point of origin designated in the open field), and time estimation in 12 experienced subjects who had, on separate occasions, ingested median oral doses of 32 mg Δ^9–THC (as a calibrated marihuana extract), 57 g ethanol, 15 mg dextroamphetamine sulfate, and placebo. Only arithmetic skill and time estimation were significantly affected by the marihuana extract.

Melges *et al.* (1970) and Tinklenberg *et al.* (1970) measured immediate or short-term memory in 8 subjects (prior drug history unspecified). Route of administration was oral; dose levels were 20, 40, and 60 mg Δ^9–THC; and a control (placebo) condition was included. Immediate memory was adversely affected, and the authors concluded that this impairment may hinder the individual's ability to compare current perceptions with memories. No consistent dose-response relationship was observed in their study.

Waskow *et al.* (1970) measured memory in 32 subjects (naive and experienced); route of administration was oral (20 mg Δ^9–THC). Little, if any, impairment of functioning was noted. Rafaelsen *et al.* (1971) measured memory and attention in 8 subjects who received oral doses of 8 to 16 mg Δ^9–THC. Decreased scores were observed only for the higher dose condition.

Darley *et al.* (1973) used a complex design which extended over 6 days with an initial oral administration of marihuana extract calibrated to provide 20 mg Δ^9–THC and subsequent doses of marihuana extract or placebo. The drug effect was explained as a change in the encoding processes of memory.

One group of investigators used both pulmonary and oral routes of administration. Jones and Stone (1970) measured muscular coordination and attention, time judgment, and general alertness in 10 heavy users of marihuana after the subjects had smoked marihuana containing 4.5 mg Δ^9–THC (with the smoking procedure unspecified) or had taken by mouth an ethanolic extract of marihuana containing 90 mg Δ^9–THC. A placebo condition was also included. Only time estimation was adversely affected after marihuana given by either route of administration.

Marihuana Research Studies at the University of British Columbia (U.B.C.)

Since 1971, a group of investigators at U.B.C. has been investigating the effects of marihuana in a variety of contexts. Studies have been conducted in the following areas: acute effects on neuropsychological functioning (Klonoff, 1973a; Klonoff *et al.*, 1973); acute effects on neurophysiological functioning (Low *et al.*, 1973); patterns of drug use and subjectively reported effects in social marihuana users and chronic marihuana users (Klonoff, 1973b; Klonoff and Clark, 1976); effects on verbalization and thought processes (Crockett *et al.*, 1976); effects on driving (Klonoff, 1974a and b); and psychiatric status of the marihuana users (Marcus *et al.*, 1974).

Neuropsychological Effects of Marihuana

Our study (Klonoff, 1973a; Klonoff *et al.*, 1973) assigned 81 non-naive subjects, divided into low- and high-dose groups, to four experimental conditions (marihuana/marihuana, marihuana/placebo, placebo/marihuana and placebo/placebo) for two sessions separated by about one week. The low dose was 4.8 mg Δ^9–THC followed by 2.4 mg one hour later. The high dose was 9.1 mg followed by 4.5 mg one hour later. A battery of neuropsychological tests was administered (Table 1). The battery consisted of 13 tests and 32 variables, since multiple measures were obtained from some of the tests. The test battery was designed to measure the following four mental processes, the sensory input being provided by a variety of modalities: (i) concept formation—visual; (ii) memory—(a) tactile, (b) auditory, (c) visual; (iii) tactile form discrimination; and (iv) motor. The duration of the examination, and of re-examination one week later, was approximately one and three-quarter hours on each occasion. The order of presentation of the tests during both sessions was randomized from one subject to another in order to reduce bias that might result from examination (or re-examination) during maximal drug effect. Whereas the curve of decay from maximal drug effect could be minimized by order of presentation of the tests, session-to-session practice effects could not be controlled but were allowed for in the statistical analysis of data. In addition, the Wechsler Adult Intelligence Scale (WAIS) and Minnesota Multiphasic Personality Inventory (MMPI) were administered. The low dose produced impairment of all mental processes (concept formation, memory, tactile form discrimination, and motor function) and the effect was generalized to all modalities (Table 2). The high dose resulted in more extensive impairment, again generalized (Table 3). The drug effects noted were explained in terms of generalized impairment of central integrative processes. The effects of marihuana on learning as well as memory were explained in terms of impaired output (recall), but the impairment was transient.

More Recent Studies of the Effects of Marihuana on Psychological Functions

Hemispheric Involvement with Marihuana

Lateralized hemispheric function during marihuana intoxication has been examined in two well designed studies. Harshman *et al.* (1976) proposed and confirmed two hypotheses concerning the psychological effects of marihuana: "(i) that the process of becoming high on marihuana consists, in part, of shifting into a new cognitive style or mode which involves less reliance on analytical, sequential, verbal processing, and more reliance on synthetic, holistic, imagistic processing; (ii) that one of the ways that marihuana produces this shift is by decreasing left, and increasing right hemisphere participation in cognitive activities." Stillman *et al.* (1977) found that moderate doses of marihuana may differentially change the processing speed or relative dominance of man's two cerebral hemispheres, depending on the nature of the material being processed.

Memory Functioning with Marihuana

A number of investigators have focused on the effects of marihuana on the various aspects of the memory process (Darley *et al.*, 1974; Dornbush, 1974; Vachon *et al.*, 1974; Borg *et al.*, 1975; Domino *et al.*, 1976; Mendelson *et al.*, 1976; Miller *et al.*, 1976; Tinklenberg and Darley, 1976; Miller *et al.*, 1977; Miller and Cornett, 1978; Miller *et al.*, 1979). Klonoff *et al.* (1973) suggested that memory output is influenced by marihuana, while the acquisition process is left largely intact. Dornbush (1974) suggested that the drug affects storage rather than the retrieval process. Miller *et al.* (1978) found that the drug appeared to exert its most deleterious effect on the retrieval of information from long-term storage. Jones (1978), in his review of the literature, found a consensus

TABLE 1[1]

Neuropsychological Test Battery

Test no.	Test Name	Stimuli	Variable no.	Score	Function	Mental Process	Description of Mental Process
1	Halstead Category	208 slides	1	No. errors	Visual	Concept formation reasoning	Requires postulation of hypotheses that appear reasonable with respect to recurring similarities and differences in the stimulus material
2	Trail Making	25 circled numbers	2 A	Time			Requires immediate recognition of symbolic significance of numbers and letters; ability to scan and identify and sequence
		25 circled numbers and letters	3 B	Time	Visual	Conceptual relations	
			4 Total				
3	Halstead Tactual Performance	10 blocks and form-board	5 Dom. hand	Time	Tactile (performed while blindfolded)	Tactile discrimination speed	Depends upon tactile form discrimination, kinesthesis, manual dexterity, visualization of spatial configuration and retention of spatial interrelationships
			6 N-dom. hand	Time			
			7 Both hands	Time			
			8 Total	Time			
			9 Memory	No. correct		Incidental learning Memory	
			10 Location	No. correct			
4	Seashore Tonal Memory	30 pairs of tonal sequences	11	No. errors	Auditory	Memory—immediate	Requires alertness and sustained attention and retention

5	Benton Sentence Repetition	26 sentences of increasing length	12	No. correct	Auditory	Memory—immediate	Requires longer span of focused attention and recall of meaningful information
6	Picture Recognition	76 common objects projected, 16 repeated	13	No. errors	Visual	Memory—immediate	Involves visual pattern discrimination and recognition of a stimulus within a serially presented series
7	Peterson Visual Memory	6 common noun trigrams projected, followed by counting 3-digit number and recall of trigram	14	No. errors	Visual	Memory—immediate	Involves retroactive interference, negative transfer, and measures the effect of an interpolated intervening activity upon the retention and recall of a stimulus
8	Halstead Finger Tapping	Mechanical finger tapper	15 Dom. hand 16 N-dom. hand	Mean of five 10-sec. trials for each hand	Motor	Undirected motor speed upper extremities	Requires motor speed for brief intervals
9	Foot Tapping	Mechanical foot tapper	17 Dom. foot 18 N-dom. foot	Mean of two 10-sec trials for each foot	Motor	Undirected motor speed lower extremities	Requires motor speed for brief intervals
10	Klove Grooved Steadiness	Vertical groove	19 Dom. hand 20 Dom. hand 21 N-dom. hand 22 N-dom. hand	Time No. contacts Time No. contacts	Motor	Directed motor steadiness	Requires gross visual-motor coordination in one plane

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[1] Originally printed in: *Can. Med. Assoc. J.*, Vol. 108, January 20, 1973

TABLE 1[1] (CONTINUED)

Test no.	Test Name	Stimuli	Variable no.	Score	Function	Mental Process	Description of Mental Process
11	Klove Maze Coordination	Maze	23 Dom. hand	Time	Motor	Dynamic motor coordination	Requires gross visual-motor coordination in multiple planes
			24 Dom. hand	No. contacts			
			25 N-dom. hand	Time			
			26 N-dom. hand	No. contacts			
12	Klove Static Steadiness	Plate with 9 holes decreasing in size	27 Dom. hand	Time	Motor	Static fine visual-motor coordination	Requires fine motor steadiness
			28 Dom. hand	No. contacts			
			29 N-dom. hand	Time			
			30 N-dom. hand	No. contacts			
13	Grooved Pegboard	25 identical grooved pegs to be fitted into grooved holes	31 Dom. hand	Time	Motor	Manipulative dexterity	Requires speed, accuracy and eye-hand coordination
			32 N-dom. hand	Time			

that memory defects during the intoxication stage of marihuana derive from alterations in storage rather than acquisition or retrieval. Jones further concluded that the duration of alterations in memory functioning was a few hours after smoking marihuana, but Jones cites a study by Gianutsos and Litwack (1976) which suggests more lasting problems with the transfer of new information into long-term memory storage.

Psychomotor Performance with Marihuana

As has been pointed out by Rittenhouse (1979), impairment of psychomotor performance by marihuana is a complex interactive function of a multiplicity of variables, including the characteristics of the sample selected, the dose of Δ^9-THC consumed, task instructions, task complexity, the experimenter's implicit expectations, the user's previous marihuana and other drug history, and the user's behavioral set. In general, infrequent users are more sensitive to impairment than regular users. Complex tasks such as those requiring undivided attention and especially those involving mental coordination of a number of factors are more affected than simple ones.

Dose-dependent decrements in motor performance have been reported in the following tasks: speed of moving the hand from one switch to another at the presentation of a visual stimulus (Borg *et al.*, 1975); hand steadiness (Milstein *et al.*, 1975); stability of stance (Dalton *et al.*, 1975); motor coordination (Steadward and Singh, 1975); and manipulation and coordination (Salvendy and McCabe, 1975).

Other investigators found that only high doses of Δ^9-THC triggered motor effects, such as tremors, increased tendon reflexes, myoclonus and shivering (Domino *et al.*, 1976; Tassinari *et al.*, 1976). But the motor anomalies and psychomotor effects were noted to be transient, and not evident beyond the period of intoxication or two to four hours thereafter. The variability in findings may perhaps be explained in terms of the differential effects of smoked and orally administered Δ^9-THC.

There is little work on the effects of other cannabinoids on human performance. Consroe *et al.* (1979) studied the effects of cannabidiol (CBD) and alcohol by means of a battery of motor and psychomotor tests. Compared with the placebo, alcohol given either alone or with CBD, but not CBD alone, produced significant impairments of motor and psychomotor performances. Belgrave *et al.* (1979) also examined the effects of CBD given orally (in capsules containing 2.5, 5.0, or 10.0 mg) alone or in combination with ethanol on a battery of tests measuring reaction speed, standing steadiness, psychomotor coordination, and cognition. There was no demonstrable effect of CBD, either alone or in combination with the ethanol. These findings differ from those reported

TABLE 2[1]

Neuropsychological Effects of Low-Dose Marihuana: Results of F Tests for Group-Analysis of Variance

Test no.	Variable no.	Test name	Between groups	Between trials	Groups x trials	Marihuana effect during initial session†	Marihuana effect during 2nd session (unrelated)††	Marihuana effect during 2nd session (related)†††
1	1	Category test (err.)	3.27*	47.77****	1.71	11.35****	0.17	1.48
2	2	Trail Making—A (time)	5.46***	7.59***	4.25***	9.28***	5.30*	1.12
	3	Trail Making—B (time)	10.37****	7.83***	4.12***	28.39****	5.25*	0.26
	4	Trail Making—Total (time)	9.96****	9.71***	4.06***	28.52****	6.57**	0.02
3	5	Tactual Performance Test—Dom. (time)	0.45	20.37****	1.05	2.21	2.71	0.30
	6	Tactual Performance Test—N-dom. (time)	1.00	8.94***	0.42	2.33	5.96**	0.23
	7	Tactual Performance Test—Both (time)	1.19	6.00**	0.55	5.73**	3.41	0.38
	8	Tactual Performance Test—Total (time)	1.05	16.92****	0.80	4.19*	5.72**	0.36
	9	Tactual Performance Test—Memory (corr.)	1.47	5.95**	0.81	3.58	0.00	2.17

	10	Tactual Performance Test—Location (corr.)	0.81	5.72**	0.38	0.31	0.01	0.44
4	11	Seashore Tonal Memory (err.)	2.62*	0.21	0.54	0.93	1.30	2.14
5	12	Sentence Repetition (corr.)	10.69****	0.07	4.04***	7.17***	14.17****	2.89
6	13	Picture Recognition—Total (err.)	0.71	2.95	0.28	2.94	0.01	0.04
7	14	Visual Memory (err.)	9.45****	7.09***	3.25*	20.89****	6.95***	0.08
8	15	Finger Tapping—Dom. (corr.)	1.09	0.10	1.25	3.52	0.13	0.23
	16	Finger Tapping—N-dom. (corr.)	1.01	0.85	0.08	1.72	0.04	0.32
9	17	Foot Tapping—Dom. (corr.)	1.00	0.31	0.18	0.24	0.65	2.91
	18	Foot Tapping—N-dom. (corr.)	1.15	0.07	0.06	0.94	0.28	0.03
10	19	Grooved Steadiness—Dom. (time)	2.09	6.52**	1.41	12.50****	0.37	1.08
	20	Grooved Steadiness—Dom. (corr.)	5.22***	4.00*	2.86*	15.06****	0.31	0.20

$*P < 0.05$; $**P < 0.02$; $***P < 0.01$; $****P < 0.001$

†$(M_1M_2 + M_1P_2)-(P_1M_2 + P_1P_2)$

††Marihuana effect during second session unrelated to experimental condition in initial session $(M_1M_2 + P_1M_2)—(M_1P_2 + P_1P_2)$

†††Marihuana effect during second session related to experimental condition in initial session $(M_1M_2-M_1P_2)-(P_1M_2-P_1P_2)$

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TABLE 2[1] (CONTINUED)

Test no.	Variable no.	Test name	Between groups	Between trials	Groups x trials	Marihuana effect during initial session†	Marihuana effect during 2nd session (unrelated)††	Marihuana effect during 2nd session (related)†††
	21	Grooved Steadiness—N-dom. (time)	0.31	2.66	0.20	1.39	1.82	1.06
	22	Grooved Steadiness—N-dom. (corr.)	0.11	2.45	0.05	0.13	0.45	2.45
11	23	Maze Coordination—Dom. (time)	0.64	3.28	0.36	1.98	3.78*	0.01
	24	Maze Coordination—Dom. (corr.)	0.57	2.80	0.37	1.77	3.01	0.02
	25	Maze Coordination—N-dom. (time)	1.14	4.45*	0.76	1.02	0.05	0.01
	26	Maze Coordination—N-dom. (corr.)	0.73	8.69***	0.38	0.69	0.24	0.27
12	27	Static Steadiness—Dom. (time)	10.43****	1.30	4.21***	12.97****	14.64****	1.32
	28	Static Steadiness—Dom. (corr.)	5.20***	0.67	1.72	3.57	10.16***	1.25
	29	Static Steadiness—N-dom. (time)	6.77****	0.15	3.17*	4.47*	8.62***	0.98
	30	Static Steadiness—N-dom. (corr.)	3.50**	0.02	2.44	1.76	8.98***	1.18
13	31	Grooved Pegboard—Dom. (time)	2.70*	2.07	1.13	1.87	8.11***	0.02
	32	Grooved Pegboard—N-dom. (time)	2.49	0.41	0.33	0.00	1.27*	0.13

by Consroe *et al.* (1979), and both studies are at variance with other reports in the marihuana literature dealing with the effects of Δ^9-THC on psychomotor performance. This is not surprising, given the low psychoactivity of CBD.

Visual Perception with Marihuana

Knowledge of marihuana-induced changes in sensory processes is important in its own right, but doubly important because these processes form part of the complex abilities required in driving.

Schwin *et al.* (1974) reported on the effects of marihuana on critical flicker fusion (CFF). CFF has been used to study the physiology of vision and refers to the minimal number of successive flashes of light per second that produces a sensation of steady light. Unlike a variety of drugs that affect the fusion threshold, smoked marihuana (containing 1.5% Δ^9–THC) raised the CFF threshold, i.e., enabled the subject to recognize the separateness of a larger number of discrete stimuli per second. This increased excitability of the visual system following marihuana smoking is discussed by the authors in the context of "perceptual sharpening."

Milstein *et al.* (1975) reported on the effects of smoked marihuana on a visual recognition task (speed of recognition). They found no statistically significant changes in performance on the visual recognition task.

Brown *et al.* (1975) found that smoked marihuana decreased dynamic visual acuity for the detection of a small moving target, but that alcohol had an even greater effect. Adams *et al.* (1975) found that static visual acuity, an easier task, was not affected by alcohol or marihuana in the doses used. Adams *et al.* (1976) investigated the effects of alcohol and smoked marihuana on color discrimination. The authors found significant dose-related impairment in hue discrimination on the Farnsworth-Munsell 100 hue test with single doses of alcohol and marihuana. The impairment of color discrimination resembled that seen with acquired color vision defects. The transient reduction of color discrimination would have ramifications in those situations which require stable color perception.

Adams *et al.* (1978) investigated the effects of smoked marihuana, alcohol, and the combined drugs on glare recovery. They found that the time course of light adaptation after intense light exposure was significantly delayed by all three conditions, but the combined alcohol and

TABLE 3[1]

Neuropsychological Results of F Tests for High-Dose Group-Analysis of Variance

Test no.	Variable no.	Test name	Between groups	Between trials	Groups × trials	Marihuana effect during initial session†	Marihuana effect during 2nd session (unrelated)††	Marihuana effect during 2nd session (related)†††
1	1	Category test (err.)	5.61****	60.06****	2.17	26.40****	4.30*	0.01
2	2	Trail Making—A (time)	2.22	0.01	1.77	5.79**	8.42***	0.09
	3	Trail Making—B (time)	7.99****	4.16*	6.21****	18.95****	17.03****	0.04
	4	Trail Making—Total (time)	7.63****	2.86	5.65****	18.48****	18.23****	0.09
3	5	Tactual Performance Test—Dom. (time)	0.75	44.32****	7.16****	16.77****	7.70***	0.14
	6	Tactual Performance Test—N-dom. (time)	1.23	14.35****	3.91***	11.57****	4.19*	1.43
	7	Tactual Performance Test—Both (time)	1.76	15.47****	1.85	5.09*	3.08	0.49
	8	Tactual Performance Test—Total (time)	3.71**	34.72****	6.27****	16.28****	7.28***	0.78
	9	Tactual Performance Test—Memory (corr.)	2.50	6.25**	1.19	3.83*	0.80	0.13

	10	Tactual Performance Test—Location (corr.)	1.27	12.73****	0.75	0.48	0.37	0.95
4	11	Seashore Tonal Memory (err.)	2.03	1.25	0.42	0.09	0.98	0.01
5	12	Sentence Repetition (corr.)	17.38****	3.63	5.58****	21.97****	3.25	1.43
6	13	Picture Recognition—Total (err.)	5.73****	2.26	3.10*	6.13**	7.58***	0.48
7	14	Visual Memory (err.)	9.33****	2.98	3.87***	15.19****	15.47****	0.15
8	15	Finger Tapping—Dom. (corr.)	5.59****	0.63	0.82	4.78*	6.58**	0.54
	16	Finger Tapping—N-dom. (corr.)	3.02*	0.51	1.32	6.79***	5.85**	0.62
9	17	Foot Tapping—Dom. (corr.)	0.90	2.15	0.36	0.94	0.00	0.32
	18	Foot Tapping—N-dom. (corr.)	0.99	0.98	0.40	2.12	1.64	0.07
10	19	Grooved Steadiness—Dom. (time)	2.94*	1.50	2.14	7.93***	5.45**	2.55
	20	Grooved Steadiness—Dom. (corr.)	2.68*	1.63	1.83	8.30***	5.00*	1.49
	21	Grooved Steadiness—N-dom. (time)	1.58	1.08	0.66	8.34***	4.62*	0.30

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*$P < 0.05$; **$P < 0.02$; ***$P < 0.01$; ****$P < 0.001$

†$(M_1M_2 + M_1P_2)-(P_1M_2 + P_1P_2)$

††Marihuana effect during second session unrelated to experimental condition in initial session $(M_1M_2 + P_1M_2)-(M_1P_2 + P_1P_2)$

†††Marihuana effect during second session related to experimental condition in initial session $(M_1M_2-M_1P_2)-(P_1M_2-P_1P_2)$

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TABLE 3[1] (CONTINUED)

Test no.	Variable no.	Test name	Between groups	Between trials	Groups × trials	Marihuana effect during initial session†	Marihuana effect during 2nd session (unrelated)††	Marihuana effect during 2nd session (related)†††
	22	Grooved Steadiness—N-dom. (corr.)	1.78	0.55	0.71	5.64**	9.21***	1.02
11	23	Maze Coordination—Dom. (time)	3.29**	1.39	2.30	10.87***	2.39	0.90
	24	Maze Coordination—Dom. (corr.)	4.14***	6.83***	2.72*	12.88****	2.06	1.60
	25	Maze Coordination—N-dom. (time)	2.92*	5.83**	2.11	4.46*	2.66	0.09
	26	Maze Coordination—N-dom. (corr.)	4.71***	4.58*	2.94*	4.67*	4.27*	0.11
12	27	Static Steadiness—Dom. (time)	2.85*	0.31	3.78**	19.57****	8.78***	1.56
	28	Static Steadiness—Dom. (corr.)	4.53***	0.10	4.31***	15.09****	11.78****	1.41
	29	Static Steadiness—N-dom. (time)	1.61	0.29	6.20****	13.20****	18.49****	0.00
	30	Static Steadiness—N-dom. (corr.)	4.70***	0.00	3.98***	10.16***	12.68****	0.06
13	31	Grooved Pegboard—Dom. (time)	25.39****	7.53***	7.64****	25.24****	2.50	0.29
	32	Grooved Pegboard—N-dom. (time)	16.28****	2.12	3.64**	18.47****	2.69	0.06

marihuana treatment produced little more than the effect produced by either drug alone.

Visual divided attention is a phenomenon that intersects more directly with driving. MacAvoy and Marks (1975) reported on the effects of smoked marihuana, alcohol, and various dose combinations of the two drugs on a divided attention task. Performance by all subjects was significantly impaired following 2.6 and 5.2 mg Δ^9–THC but not by alcohol alone at blood alcohol concentrations of 0.048% and 0.096%. The combined effect of marihuana plus alcohol was variable and depended upon prior experience with marihuana, i.e., a synergistic action occurred in the nonusers while an antagonistic effect occurred in the users.

Sustained attention or vigilance is a phenomenon that also has an important role in driving, and in visual signal detection. Sharma and Moskowitz (1974) examined the effects of smoked marihuana (200 μg/kg Δ^9–THC) on a visual sustained attentional task. They found that marihuana significantly impaired the detection of signals. Furthermore, there was a significant effect of marihuana on vigilance performance. They concluded that under the influence of marihuana, the user will initially demonstrate impaired performance of tasks that require maintained attention. This will be followed by a further performance decline over time.

2. EFFECTS OF MARIHUANA ON DRIVING

Marihuana and Driving in a Restricted Area

Studies on the effects of marihuana and other drugs on driving in real life situations are still sparse. One study that may well be a landmark is that of Coldwell *et al.* (1958), which dealt with the effects of alcohol on driving in a restricted area. One of the first comprehensive reviews of the effects of drugs on driving was published by Nichols (1971). The Commission of Inquiry into the Non-Medical Use of Drugs (Le Dain, 1972) was the first to describe the effects of two levels of smoked marihuana (1.4 mg Δ^9–THC and 5.9 mg Δ^9–THC) and a single dose of alcohol (average blood alcohol level 0.07%) on 16 subjects who drove a vehicle in a restricted traffic-free area. The Commission concluded: "The low marijuana dose and placebo conditions were not different in terms of the number of poles or road cones hit. Both the higher marijuana dose and the alcohol condition produced small increases in hits, which were reliably different from placebo, but not significantly different from each other. The higher cannabis dose resulted in a slight (7%) but consistent decrease in driving speed."

Smiley *et al.* (1975) reported a driving study in a restricted area (a 13.7 km stretch of new highway) in which the effects of various drugs given alone, of alcohol and marihuana together, and of a placebo were compared. For the combined alcohol and marihuana condition, reaction time was significantly longer than for the placebo.

Hansteen *et al.* (1976) published the final report on the driving and psychomotor tracking studies conducted by the Canadian Commission of Inquiry into the Non-Medical Use of Drugs (Le Dain, 1972). Their first experiment included 16 subjects—12 males and 4 females. The experimental conditions were: placebo (cannabinoid-free marihuana and a nonalcoholic drink); two dose levels of marihuana (delivering average doses of 1.4 and 5.9 mg Δ^9–THC); and one dose of ethanol (producing an average blood alcohol level of 0.07% 20 min after drinking the equivalent of about three cocktails). The driving course was an abandoned airplane landing strip at Rockcliffe Air Force Base in Ottawa. Driving was scored on hits of cones and poles as well as driving time. Supplementary physiological and psychological parameters were measured, including: heart rate, visual imagery, Clyde's mood scale, various scales regarding state of the "high," a test of the subject's attitudes and experiences regarding driving while high, a postsession questionnaire, and a morning-after questionnaire. The results indicated poorer car handling performance after administration of both alcohol and the higher dose of cannabis. Secondly, the time taken to drive each lap was increased after the higher dose of cannabis.

Their second experiment was designed to determine the effects of cannabis and alcohol on psychomotor tracking performance. Twenty-two male subjects each attended six weekly experimental sessions in addition to two preliminary no-drug practice sessions. The six experimental conditions were: placebo (cannabinoid-free cannabis and a nonalcoholic drink), two dose levels of cannabis (1.6 and 6.8 mg Δ^9–THC), two dose levels of alcohol (enough to produce blood alcohol levels of 0.07% and 0.03%), and the low cannabis and low alcohol doses combined. The tasks included simple tracking and complex tracking. Supplementary physiological and psychological measures were collected during each session.

Alcohol resulted in a clear dose-related increase in errors in simple tracking compared with placebo. The higher cannabis dose, but not the lower dose, also resulted in a significant increase in error scores. The combination of the low doses of cannabis and alcohol produced error scores that were not significantly different from those obtained after the low dose of alcohol. Alcohol resulted in a dose-related increase in reaction delay time, whereas cannabis did not affect this parameter.

The Department of Justice of the State of California in November 1979 was about to begin a study of the effects of marihuana, alone and in combination with alcohol, on driving performance. This study would attempt to relate blood levels of THC and alcohol to impairment of driving on a closed course provided by the Department of Motor Vehicles, and was being coordinated by Mr. Victor Reeve of the Technical Services Bureau. Dr. J.S. Ketchum, a psychiatrist who has done research with drugs in normal volunteers, was engaged as a consultant. Dr. Leo Hollister of Stanford University and Dr. Stanley Gross of the University of California at Los Angeles (UCLA) were among the co-investigators (Ketchum, 1979). No other study has been uncovered to date which has dealt with the effects of marihuana on driving in a real life situation. To date, there have been no published reports from this proposed study.*

Psychomotor Models and Driving Simulators

Most of the published studies relevant to marihuana and driving have employed a psychomotor model or some type of laboratory driving simulator. Crancer *et al.* (1969) investigated the effects of marihuana and alcohol on simulated driving with 36 subjects and in part concluded: "Subjects experiencing a social marihuana high accumulated significantly more speedometer errors than when under control conditions, whereas there were no significant differences in accelerator, brake, signal, steering, and total errors. Impairment in simulated driving performance does not seem to be a function of increased marihuana dosage or inexperience with the drug." The methodology of Crancer *et al.* (in particular the potency of the marihuana they used) has been questioned (Kalant, 1972).

Dott (1972) used a simulated risk paradigm and found that a potentially hazardous passing situation resulted in heightened cautiousness and accurate judgment of risk for the marihuana subjects, but more aggression and less adequate judgment of risk for the subjects under the influence of alcohol. Whereas decision reaction time was prolonged during nonemergency trials for both marihuana and alcohol subjects, response to emergency signals was impaired by alcohol but not by marihuana. Bech *et al.* (1973) and Rafaelsen *et al.* (1973) also used a simulator to determine the effects of oral doses of marihuana and alcohol on driving. They found that marihuana had a much stronger effect than alcohol on the estimation of time and distance; both marihuana and alcohol increased brake time and start time; alcohol increased while marihuana decreased the number of gear changes; and mean speed was not changed with either drug but variation of speed was affected by both marihuana and alcohol. Ellingstad *et al.* (1973) reported a simulator study in which marihuana influenced the accuracy of passing-time judgments but did not adversely affect risk-taking/decision-making capabilities, while alcohol affected the latter but not the former. Ladewig and Hobi (1973) also reported similar effects of marihuana on simulated driving performance.

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*Editor's Note: Two studies have recently been published on this topic: (1) Attwood, D.A. Cannabis, alcohol and driving: Effects on selected closed-course tasks. 8th International Conference on Alcohol, Drugs and Traffic Safety, p.5, Stockholm, June 15–19, 1980; (2) Attwood, D.A., Williams, R.D., Bowser, J.S., McBurney, L.J. and Frecker, R.C. The effects of moderate levels of alcohol and marihuana, alone and in combination, on closed-course driving performance. Report published by Transport Canada, pp. 69, Toronto, 1981.

Moskowitz *et al.* (1973), using the UCLA driving simulator, found a marihuana dose-related impairment in response to a subsidiary task (increase in errors of recognition and delay in response to the visual recognition task) and to an auditory signal detection task under conditions of both concentrated and divided attention.

Subsequently Moskowitz *et al.* (1976) performed two experiments to determine the effects of alcohol and marihuana on visual scanning patterns in a simulated driving situation. In the first experiment the three blood alcohol levels used were 0.0%, 0.075%, and 0.15%. Significant changes in visual search behavior including increased dwell duration, decreased dwell frequency, and increased pursuit duration and frequency were found under alcohol. A decrease in the number of fixations or dwells would reduce the driver's ability to search the environment for potential dangers or attend to the cues necessary for proper lane maintenance and heading. In the second experiment, social users of marihuana were tested after administration of placebo or enough marihuana to deliver 200 μg/kg THC. Marihuana was found to have no effect on visual search behavior.

Still another laboratory paradigm explored has been the effects of marihuana on visual tracking. Visual tracking tasks are usually divided into three categories. The first, pursuit tracking, is a divided attention task requiring the operator to keep an indicator, which is controlled by a steering device, in alignment with another indicator which moves in an irregular pattern over which the operator has no control. In the second, compensatory tracking, an indicator has to be sustained at a given position by compensatory movements to offset unpredictable displacements to which it is subjected. The third, critical tracking, is a compensatory tracking task in which the dynamics of the controlled indicator are inherently unstable. Automobile driving is one of the more important applications of tracking task results. Under actual driving conditions, an automobile driver will be confronted with combined compensatory tracking tasks.

Roth *et al.* (1973) had male volunteers perform a five-minute paced contour tracking task before and after receiving brownies containing either placebo or marihuana calibrated to a Δ^9–THC content of 20 mg. The error patterns of 19 young male subjects who received placebo and 18 who received marihuana were compared. After marihuana there was an increase in tracking error as reflected by increases in the standard deviations and absolute deviations of the error scores. Although marihuana is reputed to create a fluctuating effect, under the conditions of this experiment the variability of error scores between successive 15-second time periods in the marihuana group was not significantly greater than in the placebo group. In addition, the marihuana deficit did not change significantly with time during the task. Stoller *et al.* (1976) examined the effects of pentobarbital, Δ^9–THC, and placebo on hand-eye coordination using an undivided attention visual tracking task, critical tracking. Performance after Δ^9–THC (22.5 mg given orally) was significantly impaired ($P < 0.04$), as compared with placebo, but performance after 150 mg pentobarbital was not significantly worse than after placebo ($P < 0.08$).

The other studies of the effects of marihuana on psychomotor skills, notwithstanding the mention of driving in the titles of these articles, may be less relevant additions to our understanding of effects of marihuana on driving (Binder, 1971; Kielholz *et al.*, 1972, 1973; Franks *et al.*, 1975).

Several studies of the effects of marihuana on driving have included physiological monitoring. The relevant parts of the literature on such monitoring during driving studies are reviewed below in the context of the study by Klonoff (1974b) to be reported in Section 3.

Physiological Monitoring during Driving

The most comprehensive review in this area is that of Wilde and Curry (1970). Taggart and Gibbons (1967) reported preliminary results of EKG studies in normal London traffic and in competitive motor racing. Simonson *et al.* (1968) reviewed cardiovascular changes reported during automobile driving and point out that heart rate responds instantaneously to critical situations during driving, a 20% to 40% increase of heart rate being directly related to traffic density and critical traffic situations. Whereas more speed did not affect heart rate further, some effect was noted with driving experience. In their monitoring of five subjects during 30 min of city driving, they found that heart rate increased on the average from 70 beats per minute at rest to 95 beats per minute while driving.

Hulbert (1957) analyzed the galvanic skin responses (GSR) of 21 subjects in traffic, in terms of idealized path, driver actions, clarity of the GSR record, and amount of traffic activity along the route. A trend was noted regarding drivers' GSRs and changes in the traffic situation. Michaels (1960) continuously monitored the frequency and magnitude of GSR changes in 10 subjects in urban test routes during five traffic periods. During the continuous test run, events per minute were 2.42 and 1.71 for the two routes taken, while average GSR magnitude was 2.28 and 2.23 for the respective routes. Of the measurable responses, 95% were caused by eight types of traffic interference, the most frequent being other vehicles in the traffic stream. Taylor (1964) measured the rate of occurrence of GSR changes in 20 drivers during a range of road conditions. Taylor found significantly different rates between his subjects, but some of the differences between subjects could be accounted for by length of experience as drivers and age. There was, however, no variation in the frequency of GSR changes for the variety of road and traffic and lighting conditions sampled. He concluded that: "Driving is a self-paced task governed by the level of emotional tension or anxiety which the driver wishes to tolerate."

Physiological Monitoring during Marihuana Smoking

Another area that is relevant to the study by Klonoff (1974b) to be reported below is that of physiological monitoring during marihuana smoking in a laboratory setting. The Commission of Inquiry into the Non-Medical Use of Drugs (Le Dain, 1972) provided a most comprehensive review of the literature on the cardiovascular system. Researchers on marihuana have, however, paid less attention to autonomic measures such as GSR and respiration. One exception is Gale and Guenther (1971) who found the basal level of skin conductance to be significantly lower during the drug sessions and they relate this to a state of relaxation or sedative effect. Low *et al.* (1973) also found that GSR reactivity decreased under conditions of marihuana intoxication compared with baseline and placebo condition.

Domino (1971) reported a minor decrease in respiratory rate with smoked marihuana. Low *et al.* (1973), however, reported a slight drop in respiration rate with smoked cannabinoid-free marihuana and slight increases for their low- and high-doses of Δ^9–THC, respectively. Tashkin *et al.* (1973) found no differences in respiration rate between their placebo and oral Δ^9–THC conditions. Gostomzyk *et al.* (1973), on the other hand, found that the respiratory rate of their subjects was 20% higher under the influence of hashish than in the drug-free state.

Traffic Accidents and Marihuana

Milner (1977) points out that over a million people died in traffic accidents between 1900 and 1965, and that half of these deaths are probably attributable to alcohol. While there is insufficient reliable information regarding the relationship between accidents and drugs other than alcohol, incidence studies are becoming available which point to a potentially serious problem. One of the earlier survey studies of the effects of marihuana on driving was that of Klein *et al.* (1971). The authors reported that, of the respondents to the survey, three-quarters of occasional or former users of marihuana who drove were frank in admitting that it interfered with their abilities to judge time, speed, and distance, and that it impaired reaction speed, control of the vehicle, and response to an emergency. Smart (1974a), in a Canadian study, reported that marihuana users had twice the usual frequency of traffic accidents during the 6–12 mo before they were convicted for marihuana use. Still another study by Smart (1974b) indicated that marihuana users had approximately the same incidence of accidents under the influence of marihuana as they had under the influence of alcohol.

Other evidence has accumulated indicating that driving ability and related skills are impaired by modest doses of marihuana (i.e., doses used in a social context) (Ehrlich, 1974; Israelstam and Lambert, 1975; Thompson, 1975; Moskowitz *et al.*, 1976). Woodhouse (1974), in an American study, reviewed the role of drugs in more than 700 fatal accidents, and found: (i) 58% of the victims had used alcohol (47% had a significant blood alcohol level); and (ii) 38% of the drivers were said to have been "in contact with marijuana." Sterling-Smith (1976) investigated fatal motor vehicle accidents in the Boston area and found that 16% of the operators who were at fault admitted to having used marihuana prior to the accident but more than half of these had also been drinking alcohol.

Laboratory Compared with Real Life Driving Studies

As Jones (1978) has pointed out, automobile driving is more complex than most of the behavioral tasks studied in the laboratory. Furthermore, the nature of the interaction of perceptual, cognitive and psychomotor functions in determining driving ability is less than well understood. Jones further points out that in certain situations the cognitive impairment resulting from marihuana may have only limited impact on actual driving performance, but may simultaneously interact with marihuana-induced changes in risk taking and emotional state, e.g., aggression. Needless to say, the combination of marihuana with alcohol or other drugs would be expected to potentiate the impairment of driving. Taking into account the questionable relevance of laboratory psychomotor studies to driving, as well as the limitations in generalizing from laboratory driving simulator studies, the thrust must be to real life studies of the effects of marihuana on driving. The risk of marihuana-related accidents (nonfatal as well as fatal) will, in the final analysis, have to be assessed on the basis of driving performance and incidence rates for marihuana users compared with nonusers.

3. UNIVERSITY OF BRITISH COLUMBIA (U.B.C.) DRIVING STUDY

Channels for Initiating Research on Marihuana and Driving

The logistics for mounting a study of the effects of marihuana on driving are still so complicated as to dissuade investigators from embarking on the process. The levels of negotiation (Figure 1) include the institution where the research will be conducted, solicitors, fund-granting agencies, Food and Drug Directorate (or equivalent agencies in other countries), various levels of law enforcement, and insurance companies (Klonoff, 1974a and b).

Purposes and Methods of Study

Purposes

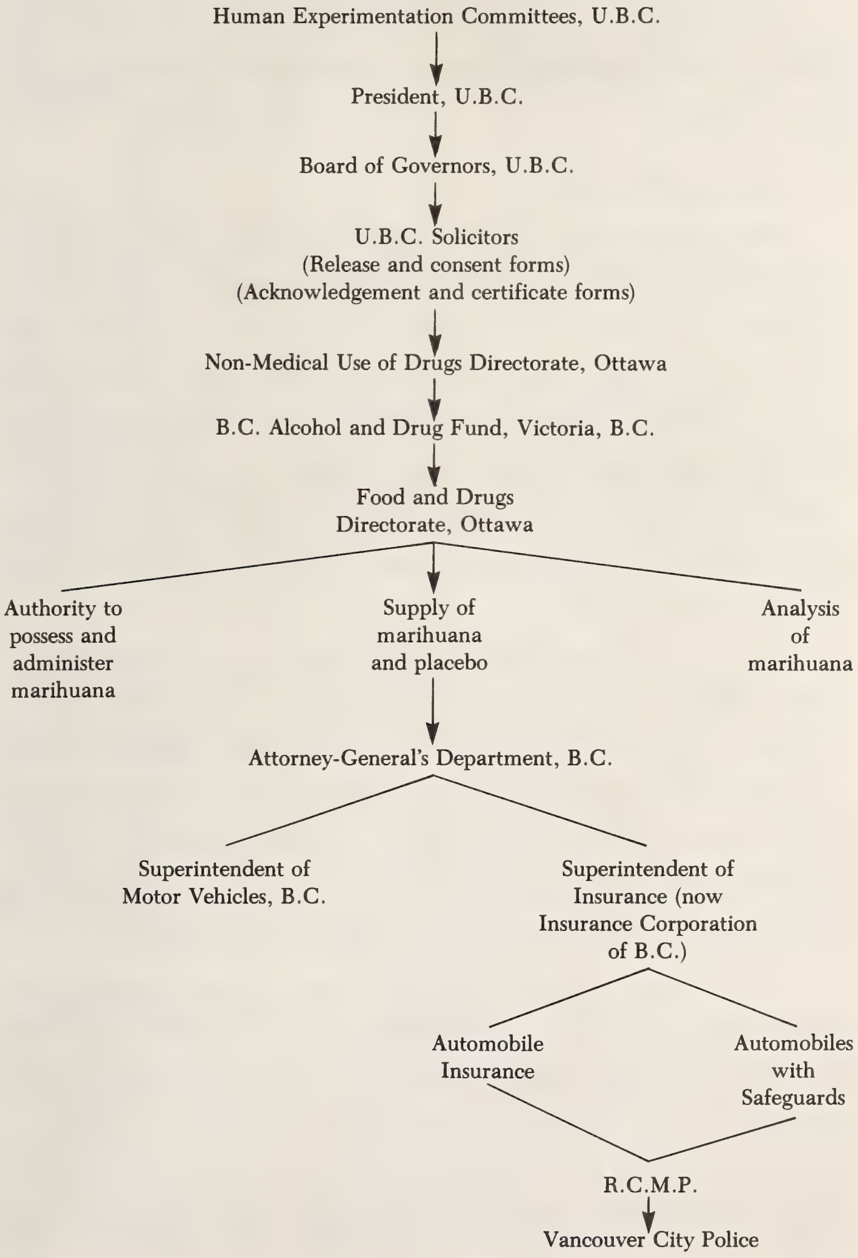
The purposes of our study were to determine: (i) the effects of low and higher doses of marihuana on driving performance in a) a restricted, traffic-free area, i.e., a driving course, and b) on the streets of Vancouver, including the downtown area, during peak hours of traffic flow; and (ii) the effects of marihuana on physiological responses, i.e., heart rate and GSR, during these driving experiences.

Subjects, Marihuana Doses, and Safeguards

For the driving course portion of the study, 64 volunteers (43 men and 21 women with a mean age of 23.9 yr) were assigned to one of three groups as follows: a group that smoked a low dose of the drug (4.9 mg Δ^9–THC); a group that smoked a higher dose of the drug (8.4 mg Δ^9–THC); and a group that smoked cannabinoid-free placebo. Of these volunteers, 38 (25 men and 13 women) also participated in the street-driving portion of the study, and were assigned to one of four groups as follows: a group given the low dose of the drug prior to the first driving session and then placebo prior to the second session; a group given placebo first and then the low dose of the drug; a group given the higher dose of the drug then placebo; and a group given placebo then the higher dose of the drug. The drug and placebo correlations were accordingly

FIGURE 1

Channels for Initiating Research on Marihuana and Driving


Human Experimentation Committees, U.B.C.
President, U.B.C.
Board of Governors, U.B.C.
U.B.C. Solicitors
(Release and consent forms)
(Acknowledgement and certificate forms)
Non-Medical Use of Drugs Directorate, Ottawa
B.C. Alcohol and Drug Fund, Victoria, B.C.
Food and Drugs Directorate, Ottawa
Authority to possess and administer marihuana
Supply of marihuana and placebo
Analysis of marihuana
Attorney-General's Department, B.C.
Superintendent of Motor Vehicles, B.C.
Superintendent of Insurance (now Insurance Corporation of B.C.)
Automobile Insurance
Automobiles with Safeguards
R.C.M.P.
Vancouver City Police

counterbalanced for each subject for each session. A double-blind procedure was maintained for both the street and the course portions of the study.

The vehicle used on the course had dual brakes and an auxiliary ignition, and the vehicle used for the tests on city streets had dual steering wheel, dual brakes, and auxiliary ignition. A trained observer was always present in the front seat of the vehicle during the study procedures.

Driving Procedures

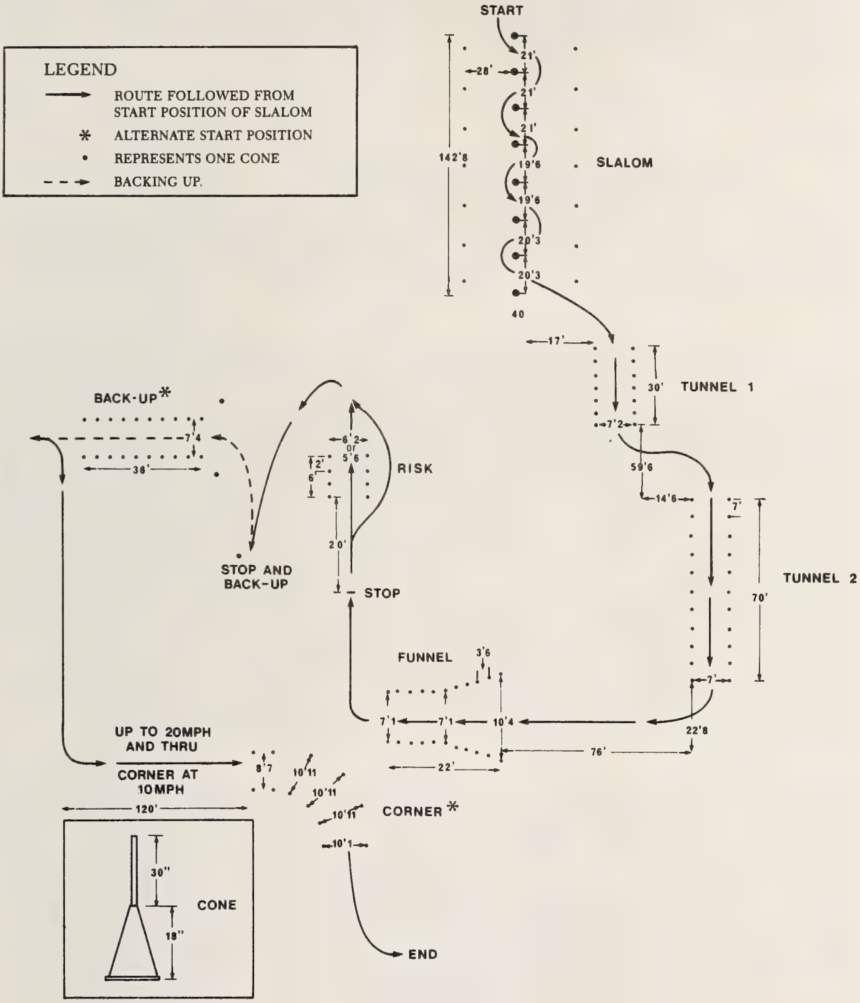
The driving course was made up of eight road tests arranged in sequence on a T-shaped paved area of about 50,000 sq ft. The course, in terms of the seven tasks, distances, and cones, is shown in Figure 2. For the driving procedure on the streets of Vancouver, the subject was instructed to drive to a designated intersection in the center of the downtown area. After arriving at this point, the subject was instructed to drive to another designated intersection in a residential area, and after arriving there, was instructed to drive back to the university hospital. The approximate distance was 16.8 miles and driving time was on the average 46 min. Driving took place during daylight hours on weekdays, and the time of day of the two sessions for each subject was standardized (traffic conditions encountered by individual subjects were accordingly more or less controlled).

On the course portion of the study, each cone hit was recorded as 1 point, except on the slalom and risk sections. For the slalom section (Figure 2), the scoring was as follows: 1 point for touching a cone; 2 points for a direct hit and knockdown of a cone; and 2 points for backing up to avoid hitting a cone. For the risk section (Figure 2), the scoring was as follows: for the smaller gap, 0 points for driving around it and 4 points for driving through it; for the larger gap, 4 points for driving around it and, depending on the number of side hits, 0, 2, or 4 points for driving through it. The scoring was done by four persons who were able to count the cones contacted by the vehicle as it traversed the course.

On the street portion of the study, the format for scoring was derived from the driver's examination set by the British Columbia Department of Motor Vehicles. Eleven behavioral components involved in driving were selected and quantified. The components reflecting driving skills and their respective raw score ranges were as follows: (i) General driving habits, including: posture (0 to 5); starting and stopping (0 to 5); carelessness with driving regulations (0 to 10); turning (0 to 10); lane changing (0 to 10); regard for traffic signals (0 to 10); poor driving habits, e.g., turning the head while talking (0 to 10). (ii) Cooperation (0

FIGURE 2[1]

Plan of Driving Course


LEGEND
ROUTE FOLLOWED FROM START POSITION OF SLALOM
✻ ALTERNATE START POSITION
• REPRESENTS ONE CONE
BACKING UP.
START
21'
28'
21'
21'
19'6
19'6
20'3
20'3
142'8
SLALOM
40
17'
30'
TUNNEL 1
7'2
59'6
14'6
7'
TUNNEL 2
70'
7'
22'8
76'
BACK-UP✻
7'4
36'
STOP AND BACK-UP
6'2 or 5'6
2'
6'
RISK
20'
STOP
FUNNEL
3'6
7'1
7'1
10'4
22'
UP TO 20MPH AND THRU
CORNER AT 10MPH
120'
8'7
10'11
10'11
10'11
10'1
CORNER✻
END
30"
CONE
18"

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[1] Originally published in: *Marijuana: Effects on Human Behavior*, Miller, L.L. (ed.), Academic Press, Inc., New York, 1974.

to 5). (iii) Attitude (0 to 5). (iv) Irritability (0 to 5). (v) Judgment (0 to 5). (vi) Speed: too fast (0 to 5) or too slow (0 to 5). (vii) Care while driving: careless (0 to 5) or overcautious (0 to 5). (viii) Confidence: overconfidence (0 to 5) or lack of confidence (0 to 5). (ix) Tension: tense (0 to 5) or lethargic (0 to 5). (x) Aggression: aggressive (0 to 5) or passive (0 to 5). (xi) Concentration: fixation (0 to 5) or attention wandering (0 to 5). The driving observer assigned a raw score to each category at the end of each session.

Results

Driving Skills on Course and Street

Our first finding was that marihuana did interfere with driving skills in a restricted area, and that the effects on driving were dose-related (Table 4).

It would be misleading, however, to infer that marihuana had an invariate effect on the driving skills of this group of 64 volunteers. In the restricted driving area, 33% of the low-dose group and 55% of the high-dose group showed significant declines in performance, 43% and 31% of the respective groups did not change significantly, and 24% and 14% improved to a significant extent. How does one explain these findings? First, there are individual differences regarding drug effect, notwithstanding dosage level. Second, a change in sensorium is apt to result in efforts at compensation, particularly in driving which does require a higher degree of alertness. But as with drug effect, there are individual differences in ability to compensate, as exemplified by those volunteers whose scores did not change significantly, or in fact to over-compensate, as reflected by those subjects who showed improvement in scores.

In comparing course skills in a restricted, traffic-free area with driving and road performance on city streets, including downtown area, during peak hours of traffic flow, it should be borne in mind that the driving skills measured in these two experimental situations do not on the surface appear to be similar, and the scoring systems are certainly conceptually different. But the same trend was evident and highly consistent in the scores on both tasks. Accordingly, our second finding was that marihuana interferes more with driving performance in a real life situation than in a restricted area, although both measures are affected in a dose-related manner (Table 4). More drivers demonstrated a significant decline in driving skills on the street compared with the test course, i.e., 42% compared with 33% for the low-dose group and 63% compared with 55% for the high-dose group. The proportion that was significantly improved on the street was also consistently higher than the proportion demonstrating improvement on the course for both the low-dose group

TABLE 4

Frequency (f) and Percentage of Decline, No Change, Improvement, Significant Decline (+ 6 or more for course and 47 or higher for street), No Change (+ 5 to –5 for course and 42 to 46 for street), and Significant Improvement (–6 or less for course and 41 or lower for street) in Driving Performance on the Course and on City Streets

Change in Performance	Course (N = 64)						Streets (N = 38)			
	Placebo		Low Dose		High Dose		Low Dose		High Dose	
	f	%	f	%	f	%	f	%	f	%
Decline (+)	5	24	12	57	16	73	10	53	15	79
No change (0)	1	5	1	5	1	4	1	5	1	5
Improvement (–)	15	71	8	38	5	23	8	42	3	16
Significant decline	3	14	7	33	12	55	8	42	12	63
No change	10	48	9	43	7	31	5	26	4	21
Significant improvement	8	38	5	24	3	14	6	32	3	16

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[1] Originally published in: *Marijuana: Effects on Human Behavior*, Miller, L.L. (ed.), Academic Press, Inc., New York, 1974.

(32% compared with 24%) and the high-dose group (16% compared with 14%). In contrast, the proportion that showed no change was lower on the street compared with the course, i.e., 26% compared with 43% for the low-dose group and 21% compared with 31% for the high-dose group. On the street, as well as on the course, individualized responses to drug effect and varying degrees of compensation would account for the pattern of change in driving performance within dosage levels, with the more striking changes in impairment occurring with the high dose.

Those behavioral components most adversely affected by the drug during driving on the street were judgment and concentration, whereas those components that were affected to a lesser degree included general driving skills, irritability, speed, confidence, tension, and aggression. Furthermore, there was a significantly higher incidence in the frequency of occurrence of emergent events, but not in the degree of hazard (magnitude of events), for the drug condition compared with the placebo trials.

Physiological Measures on Course and Street

The association between autonomic arousal, emotion, and stress (Lacey and Lacey, 1970) is well accepted. Of vital functions affected during stress, heart rate shows the most dramatic and readily measurable changes. The significant and consistent changes in heart rate recorded in this study could most readily be related to an interaction model of stress-habituation and the effects of the drug.

If one began with the premise that driving on the street as well as on the course was stressful and would have resulted in autonomic activation, and predriving baseline differences for the course and street were ruled out, then the significant increase in heart rate noted on the course (30%) compared with the negligible (6%) increase on the street could be explained in terms of the monitoring procedure and habituation. The smoking of marihuana potentiated the stress of driving, and subjects who drove on the street and those who drove on the course showed an almost identical degree of tachycardia (further increases in the order of 22% above the heart rate during driving in the drug-free state). However, this effect appeared to be dose-dependent in only 4 of the 11 test conditions in the street driving, and not in any of the test conditions on the course.

The findings in this study with respect to GSR are less striking than the heart rate measure, but the stress-habituation-drug model is still applicable. In comparing GSR fluctuation rates on the course and in the street, the differences are equally striking and are of the same order of magnitude for the placebo as for the drug conditions; the ratio of fluctuations was 4:1 for the course compared with the street regardless of placebo or drug conditions. On the course, only the placebo group showed a trend toward habituation. On the street, there was a dose-related response.

Subjective Impressions of Effects of Marihuana on Driving

Marihuana users report that their driving ability is adversely affected (Dalton *et al.*, 1975; Thompson, 1975). In the study by Klonoff (1974b), 61% of the group reported that marihuana slightly detracts from or impairs driving. The subjective statements regarding effects after smoking were categorized as follows: unpleasant, e.g., anxious, less attentive, slower reflexes, poor judgment, bothered by light, lack of control; pleasant, e.g., drive more slowly, relaxed, enjoy driving more, drive more skillfully. The ratio of unpleasant to pleasant effects was 60:40. In spite of the subjective awareness that marihuana detracts from or impairs driving, 80% of the subjects studied by Klonoff (1974b) reported driving after having smoked marihuana and 55% admitted to smoking while driving. Smart (1974b) in a survey also found a similar incidence of marihuana use before driving.

Conclusions

(i) The effect of marihuana on driving is not uniform for all subjects but is, in fact, bi-directional; whether or not a significant decline occurs in driving ability is dependent on the dose of marihuana and on the subject's capacity to compensate for the effects of the drug. For those subjects who improved their performance, the explanation may lie in overcompensation and possibly the sedative effect of the drug.

(ii) Whereas the street portion of this study approximated normal driving conditions, it should be stressed that the context of the driving experience even on city streets was experimental. The design of this study provided maximal safeguards in terms of a dual-control vehicle and a driver observer, and, in addition, the subjects were professionally screened and with rare exception were emotionally stable. Given the experimental setting and set, safeguards, and the nature of the study sample, idiosyncratic behavior that might occur under normal driving conditions would be less likely to occur under these conditions.

(iii) Other factors might enhance the effects of marihuana on driving. The first is night driving, which may be more stressful. A second and even more important unanswered question is that of the cumulative effects of alcohol and marihuana on driving. Third, the doses of marihuana used in this study were within the range of social marihuana usage; under natural (i.e., nonexperimental) conditions, more heroic doses might be taken before driving. Fourth, the effect of marihuana on reactions and decisions made during high speed driving is still unknown.

4. THE EFFECTS OF MARIHUANA ON FLYING

The effects of marihuana on flying are potentially much more serious than on driving. Janowsky *et al.* (1976) were the first investigators to study the effects of marihuana intoxication on the ability of 10 certified airplane pilots to operate a flight simulator. The authors used a randomized double-blind crossover design to compare the effect of active vs placebo marihuana. They found that all 10 pilots showed a significant impairment of flying performance 30 min after smoking active marihuana. For a group of 6 pilots tested sequentially for 6 hr, a nonsignificant decrease in flying performance continued for 2 hr after smoking the active drug. The authors concluded that the effects of marihuana on flying performance may represent a sensitive indicator of the drug's psychomotor effects. Judging from the responsibilities of a pilot and from the available evidence to date, flying an aircraft while marihuana-intoxicated is clearly dangerous.

5. SUMMARY AND CONCLUSIONS

The most cogent summaries of the acute effects of marihuana on mental processes have been provided by Jones (1977, 1978) and updated by Rittenhouse (1979): (i) a host of studies have reported impaired functioning on a variety of cognitive and performance tasks while marihuana-intoxicated; (ii) for the most part, impairments were dose-related; (iii) as research designs become more sophisticated, evidence is accumulating that interactions between dose and task difficulty are such that performance on some cognitive tasks might even improve when low doses are used; (iv) greater appreciation has developed for the need to study a range of doses on a variety of cognitive tasks before trying to describe the effects of marihuana. There are apt to be multiple marihuana effects depending on dose and the exact demands of the task; (v) incentives to perform well (more money for correct responses) can decrease some marihuana effects; (vi) in general, investigators using the smallest doses of marihuana have reported the fewest effects; (vii) impaired memory, altered time sense and decrements in performance on a number of tasks —such as those involving reaction time, concept formation, learning, perceptual motor coordination, attention and signal detection—are commonly described in the literature; (viii) a number of discussions of the locus of the memory impairment are available. There is a growing consensus that the memory defect is due to an alteration in storage rather than acquisition or retrieval; (ix) in most laboratory studies, the duration of measurable memory alterations is a few hours after a smoked marihuana cigarette. However, there may be lasting problems with transfer of new information into long-term memory storage for some marihuana smokers.

Retrospective paradigms for determining the effects of marihuana on driving include: self-reported experiences and perceptions of users, anecdotal reports by investigators, and data collected after accidents or traffic violations. There is a general consensus that (i) marihuana does detract from or impair driving; (ii) even though marihuana does impair driving, many reports lack (experimental) evidence; and (iii) there is increasing evidence that marihuana, used alone or in combination with other drugs (particularly alcohol), is directly implicated in traffic accidents and fatalities.

Prospective paradigms include: psychomotor tasks that are presumed or known to be related to driving skills, driving simulators, traffic-free courses, and road tests. The following conclusions can be made: (i) psychomotor studies can only examine specific subsets of the complexity of behavioral demands for driving. While many such studies report dose-related findings, there is a real question about generalizing to driving *per se*; (ii) driving simulators have the advantage of enabling control of variables, but are nevertheless experimental artifacts. The studies to date have operationally defined variables such as speed errors, accelerator errors, brake errors, risk-taking in terms of passing, passing-time judgments, and visual signal detection. Whereas dose-related effects have been reported, here again there is a question about generalizing to driving *per se*; (iii) there is a desperate need for replication of studies showing dose-related effects; (iv) the dose-related effects reported derive from the one and only study that has been completed to date.

Investigators should turn their attention to: (i) driving studies on city streets, in urban areas; (ii) replication of relevant published studies; (iii) including alcohol in the experimental paradigm; and (iv) including night as well as day driving as a variable.

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Chronic Effects of Cannabis on Human Brain Function and Behavior

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1. INTRODUCTION

The possibility that chronic marihuana use may adversely affect human CNS function and behavior stimulated considerable attention in North America more than forty years ago (Walton, 1938). In the early experimental studies of the effects of repeated marihuana administration (Siler *et al.*, 1933; Mayor's Committee on Marihuana, 1944; Williams *et al.*, 1946), limitations in the design with respect to dose control and precision of measurements seriously compromised both the interpretation and generality of the research findings. No further repeat-dose studies were conducted in the United States until the decade of the 1970s, following acquisition of data describing acute marihuana effects in humans (Clark and Nakashima, 1968; Weil *et al.*, 1968; Clark *et al.*, 1970; Hollister and Gillespie, 1970; Melges *et al.*, 1970a and b; Waskow *et al.*, 1970). Those groups studying acute marihuana administration reported relatively benign effects. However, some data indicated that adverse effects may occur in chronic users (Dally, 1967). Meyer *et al.* (1971) found that casual users of marihuana showed a greater degree of impairment on perceptual and psychomotor tasks than did heavy users. Heavy users experienced more profound subjective effects within 30 min of smoking, but were less intoxicated than casual users one hour later.

Prior to the 1970s relatively little well-controlled systematic inves-

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tigation was conducted to assess the effects of chronic marihuana use by humans. As late as 1972, comprehensive and critical reviews of marihuana (Grinspoon, 1971; Hollister, 1971; Snyder, 1971) revealed that all but three of the experimental studies of the effects of marihuana on human behavior focused only upon the effects of single doses of the drug. At about this time, a report by Campbell *et al.* (1971) aroused great concern that marihuana use by young adults might increase the risk of structural damage to the CNS. Pneumoencephalographic studies in 10 young men reporting a past history of heavy marihuana use were reported to reveal considerable evidence of cerebral atrophy. Since these subjects had either a neurological disorder or cognitive impairment, there was a possibility that they represented the risks that might be incurred by a very small proportion of heavy marihuana smokers. However, the case histories described by the authors suggested that other factors such as antecedent head trauma or other neurological problems might account for the abnormal pneumoencephalographic findings. Because of the discomfort and potential risk of pneumoencephalographic examination, similar studies evaluating the possible deleterious effects of marihuana smoking on the structural integrity of the CNS were not performed until 1977. Kuehnle *et al.* (1977) and Co *et al.* (1977) were able to carry out accurate examination of the brain structure of chronic marihuana users with the recently developed noninvasive technique of computerized axial tomography (CAT). These studies revealed no atrophic changes as determined by CAT scanning in the CNS of heavy marihuana users as compared with normal controls.

Thus, in at least one instance, purported structural damage to the CNS by marihuana was not confirmed in studies employing technological refinements and more adequate controls. As a corollary to this situation, it can be anticipated that some of the less serious toxic effects attributed to chronic marihuana smoking may also be disproved in future studies which utilize more rigorous and sophisticated experimental design and methods.

The purpose of this chapter is to highlight data that have been obtained during the past decade on the chronic effects of cannabis on human CNS function and behavior. Although much work has been done in this area, any conclusions that can be reached at this time are at best fragmentary and tentative. It cannot be emphasized too strongly that there remain enormous lacunae in our information about marihuana effects in humans. For example, the literature search for this review did not locate a single study that systematically evaluated the behavioral and CNS effects of chronic marihuana use by women in a controlled research ward environment (analogous to studies carried out with male volunteers). Even the chronic studies carried out with males under well-controlled research conditions are relatively few in number. It is therefore to be hoped that the decade of the 1980s will produce much more complete information about the effect of chronic cannabis use on humans. Much of this information will undoubtedly come from serendipitous clinical case observations. It is also hoped that well-designed and controlled clinical research investigation will complement such information.

2. MARIHUANA AND PSYCHOPATHOLOGY

Some clinicians have implicated marihuana in the development of certain biochemical changes in the CNS (Kolansky and Moore, 1972), cerebral atrophy (Campbell *et al.*, 1971), and depression and paranoia (Keeler, 1967). Concern about possible persistent changes in mental status and behavioral patterns after marihuana use has stimulated considerable research on these issues.

Unfortunately, knowledge of marihuana effects has, until recently, been limited to case study reports and anecdotal accounts. Case study reports suffer from several serious methodologic deficiencies, including the use of selective nonrepresentative samples (Altman and Evenson, 1973) and the lack of an adequate control population. Grinspoon (1970) has observed that the prevalence of "cannabis psychosis" does not differ significantly from the prevalence of psychosis found in general population surveys. Similarly, in a study of the "amotivational syndrome," Kupfer *et al.* (1973) concluded that impaired motivation may reflect depressive episodes rather than drug-induced changes. The role of preexisting depression as a determinant of behavior often associated with chronic marihuana use has been more fully discussed by Halikas (1974).

Although data that implicate marihuana as a cause of psychiatric or behavioral disturbances are not compelling, evidence suggesting that marihuana has no adverse psychiatric effects also requires rigorous scrutiny. Questionnaires specifically designed to elicit information about previous experience of adverse drug effects may be selectively answered by subjects who enjoy the effects of marihuana and have positive attitudes about its use. Studies that assess neurophysiological or psychiatric effects of marihuana on college students either implicitly (Robbins and Tanck, 1973; Culver and King, 1974) or explicitly (Marcus *et al.*, 1974) select healthy subjects, in whom adverse reactions or residual drug effects are minimal. To complicate matters further, subjects who clearly enjoy the drug are most readily available as research subjects, a self-selection process that is often difficult to circumvent.

In the relatively few studies in which reasonable control group procedures were employed or where sampling bias was not a critical factor, the incidence of marihuana-related adverse reactions appeared to be very low. No impairment in abstract thinking, concentration, perception, or learning capacity was found in a prisoner population of heavy cannabis users given a battery of tests sensitive to brain dysfunction (Bruhn and Maage, 1975). Kroll (1975) treated only five patients who were psychiatrically incapacitated by marihuana use from a population of 45,000 American troops in Thailand. Bialos (1970) reports only one case of marihuana-related social breakdown during an entire year at a university mental health clinic.

In addition to the ambiguities that arise from methodologic problems, other variables may also militate against any clear conclusions about chronic marihuana effects. Psychoactive drugs have complex pharmacological properties that may interact with nonpharmacological variables, such as personality, social and cultural context (Cappell and Pliner, 1973), prevailing mood at the time of drug use (Carlin *et al.* 1972), dose, potency, route of administration, and the expectations of the user (Carlin *et al.*, 1972). It is little wonder, then, that despite recent attempts to describe chronic effects of cannabis, there remains a significant lack of consensus among researchers in the area.

There is somewhat more agreement on the acute behavioral effects of the drug, although here, too, nonpharmacological variables may play a significant role. Marihuana has been shown to influence short-term memory (Darley *et al.*, 1974), selective attention (Dittrich *et al.*, 1973), time estimation (Carlini *et al.*, 1974), and pain perception (Hill *et al.*, 1974). Subjects have been described as apprehensive, euphoric (Adams, 1942), sedated (Hollister *et al.*, 1968), and dizzy (Waskow *et al.*, 1970) after acute administration of marihuana. It is unclear whether such subjective states are considered "adverse" or are the positively reinforcing elements that ensure continued drug use.

In view of the confusion that still surrounds the pharmacological status of marihuana, there is a clear need for research in which subject history is available, the tetrahydrocannabinol (THC) concentration in the marihuana is known, and data can be collected over a period of time in a relatively controlled environment.

Greenberg *et al.* (1976) administered the Current and Post Psychopathology Scale (CAPPS) to a group of 12 moderate and 15 heavy marihuana users studied in a controlled research ward environment. Presmoking baseline scores of the psychiatric assessment scale (Table 1) show that average scores for both groups were well within the range of a normal psychiatric profile. Within the selected sample of subjects with a 5-yr smoking history, no significant signs of psychopathology were noted. However, the casual user group scored higher than heavy users on

TABLE 1

Current and Past Psychopathology Scales (CAPPS)

	Moderate Marihuana Users (n = 12)		Heavy Marihuana Users (n = 15)	
	Presmoking Baseline	Last Week of Smoking	Presmoking Baseline	Last Week of Smoking
Somatic concern	1.13	1.75*	1.20	1.40
Elated mood	1.38	2.21	1.47	2.27*
Anxiety	1.25	1.71	1.17	1.27
Depression	1.58	1.96	1.20	1.37
Guilt	1.00	1.00	1.00	1.00
Suicide	1.08	1.21	1.00	1.00
Social isolation	1.88	1.67	1.00	1.03
Suspicion	1.42	1.83	1.03	1.17
Grandiosity	1.38	1.42	1.00	1.00
Hallucinations	1.17	1.00	1.00	1.00
Routine-leisure time impairment	1.42	2.50	1.07	2.17*
Belligerence	1.33	1.67	1.07	1.47
Retardation-lack of emotion	1.71	1.92	1.23	2.43*
Agitation	1.38	1.83	1.43	1.57
Disorientation	1.00	1.33	1.00	1.00
Delusion	1.17	1.17	1.00	1.00

*$p < 0.05$

11 of the 16 assessment categories during the predrug baseline period, whereas the heavy users scored higher than casual users on only three of the categories (two were ties), but the differences between the two groups were clinically minor.

Prolonged marihuana consumption resulted in few category changes in the CAPPS. Casual users showed a small but significant change in somatic concern, possibly attributable to the relative lack of stimulation on the ward. Heavy users did not show this effect. Three changes in the heavy user group (increase in elated mood, increased routine-leisure time impairment, and increased lack of emotion), were significant but small from a clinical viewpoint.

The changes in affect and leisure time impairment have also been noted by others. For example, in a four-year longitudinal study of college student marihuana users, Brill and Christie (1974) found that a smaller percentage of regular users sought advanced degrees as compared with nonusers or occasional users. Only 6% of nonusers reported a deterioration in their emotional state over the previous four years versus 10% of regular users and 20% of those who had smoked seven or more years. These findings suggest either that regular marihuana use results in affective problems or that people with emotional problems may use more marihuana than others. As in the Greenberg *et al.* (1976) study, Brill and Christie (1974) reported that the changes were minor. They concluded that there was no general relationship between the degree of marihuana use and the emergence of impaired adaptability.

Reports that ascribe a distorted time sense following marihuana use have been inconsistent. In some cases, errors of estimation were consistent up to 4 hr postdrug and were independent of the time estimated (Hollister and Gillespie, 1970), whereas in other reports, time judgment was distorted in only one of two testing procedures (Jones and Stone, 1970). The general consensus now appears to be that in both humans (Clark *et al.*, 1970) and chimpanzees (Conrad *et al.*, 1972), administration of marihuana or Δ^9-THC results in overestimation of time; the effect is rather weak, however. Carlini *et al.* (1974) report that when feedback is introduced into the session, time estimation after THC administration returns to control levels.

3. MARIHUANA AND MOOD

Marihuana users commonly report that they smoke marihuana to induce pleasant subjective mood states (Freedman and Rockmore, 1946 a and b; McGlothlin and West, 1968; Haines and Green, 1970; Mizner *et al.*, 1970). However, data from controlled studies indicate that mood change following marihuana use may be in the direction of either euphoria or dysphoria and may vary widely in degree (Siler *et al.*, 1933; Bromberg, 1934; Williams *et al.*, 1946; Hollister *et al.*, 1968; Melges *et al.*, 1970a and b; Pillard, 1970; Meyer *et al.*, 1971; Pillard *et al.*, 1974). This variation has been attributed to a number of factors including dose, route of administration, environment, personality, previous marihuana experience and expectations of the subject (Weil *et al.*, 1968; Grinspoon, 1971; Hollister, 1971; Tart, 1971). Many investigators stress the influence of set and setting in interpreting the results of their studies (Jones and Stone, 1970; Jones, 1971; Galanter *et al.*, 1974). However, in other studies, self-ratings of marihuana intoxication were found to be unaffected by whether subjects watched television, listened to rock music, or engaged in conversation following marihuana smoking (Rossi *et al.*, 1974) or by whether subjects smoked in neutral or psychedelic environments (Cappell and Pliner, 1974). The presence or absence of music was found to have no influence on either responses to the Subjective Drug Effects Questionnaire or observer ratings of mood following oral ingestion of THC (Waskow *et al.*, 1970). Similarly, self-ratings on a sadness-happiness scale obtained from subjects smoking marihuana in neutral and favorable environments were not differentiable (Hollister *et al.*, 1975).

One group of investigators studied the interactive effects of several variables on self-ratings of intoxication obtained from experienced marihuana users (Carlin *et al.*, 1972). The variables were the amount of THC in the marihuana cigarettes (0, 7.5, 15 mg), the subject expectancy (placebos which the subjects were told either inhibited or potentiated the effects of marihuana were administered), and the modeling behavior of an experimenter accomplice who smoked a placebo marihuana cigarette and acted either intoxicated or unaffected in the presence of subjects. The results of the study indicated that the self-ratings of intoxication were affected by modeling behavior and subject expectancy at the moderate dose level (7.5 mg) but not at the zero dose and high dose (15 mg) levels. However, in a later study in which the same investigators employed only the zero and moderate dose (7.5 mg) levels, the self-ratings of intoxication obtained from naive marihuana users were found to be unaffected by the modeling behavior of the accomplice at either dose level (Carlin *et al.*, 1974). A tentative hypothesis was offered attributing the difference in results obtained from naive and experienced users to a socialization process by which individuals learn to discriminate and label their subjective drug experiences.

The importance of cognitive sets to psychopharmacological research has been underscored in a conceptual model developed by Schacter and Singer (1962). This model, which has been found useful in interpreting results in some recent marihuana research (Cappell and Pliner, 1974; Rossi *et al.*, 1974), predicts that subjective effects of psychoactive drugs will result from an interaction between pharmacological effects and situationally determined cognitions.

Many studies have failed to document the existence of a consistent relationship between marihuana use and specific antecedent or consequent mood states (Siler *et al.*, 1933; Bromberg, 1934; Williams *et al.*, 1946; Melges *et al.*, 1970a and b; Pillard, 1970; Meyer *et al.*, 1971; Pillard *et al.*, 1974; Hollister *et al.*, 1975). Rossi and his associates (1974) found that there was a small increase in ratings in a euphoric direction before subjects began smoking marihuana (compared with routine ratings) and a further small increase 30 min after smoking marihuana. One possible interpretation of this finding is that subjects may experience a rise in euphoric mood in anticipation of smoking marihuana, and this may be one of the reasons that consistent before-after differences have not been found in previous studies.

Although statistically significant, the actual quantitative increase in euphoric mood ratings found by Rossi *et al.* (1974) between the successive ratings was small compared with the increase in the intoxication ratings. This suggested that the increase in euphoric mood ratings was not linearly related to the increase in level of intoxication. The results of a subsequent analysis of the correlations between intoxication ratings and mood ratings for individual subjects supported this suggestion. This apparent lack of a linear relationship suggests that whatever effect marihuana use may have on moods, the effect cannot be attributed solely to the pharmacological action of the drug and that other variables, yet to be identified, are involved.

Social learning theories have suggested the identity of one class of variables that may be involved (Schacter and Singer, 1962; Tart, 1971; Orcutt and Briggs, 1975). The common thread in these theories is a belief that social expectations and definitions, rather than pharmacological factors, are primary determinants of subjective effects of drugs. Applied to marihuana, these theories hold that marihuana users learn from others to associate the various cues emanating from marihuana use with pleasant subjective feelings. These theories help to explain why naive users often do not experience the euphoric high even with high doses of THC, whereas experienced users may experience the high even with placebo marihuana (Jones and Stone, 1970) or with small doses of THC (Weil *et al.*, 1968). However, although these theories provide an explanation of why marihuana users describe the marihuana experience as pleasant, they do not explain why their descriptions of specific mood effects are not more uniform. Further, these theories seem to imply that marihuana has no unique pharmacological effects and that a similar euphoric feeling may become associated with any mild drug through the social learning process.

An intriguing possibility is that while marihuana use does not lead to either a specific configuration of mood states or consistent changes in specific moods, it may lead to a greater harmony of mood with the prevailing mood of others in the same social setting. As a conjecture, it may be that this harmony gives rise to a feeling of oneness with others (of being *simpático*), and this feeling is the euphoric reinforcer for marihuana use. This conjecture is consistent with the suggestion that marihuana is sociogenic (Goode, 1969) in that it is used primarily in group settings by close friends who perceive the use of marihuana as a pleasurable social activity (Haines and Green, 1970; Abelson *et al.*, 1972; Jessor *et al.*, 1973; Kandel, 1973; Fisher and Steckler, 1974).

However, since the mood effects of several other drugs have been reported to be influenced by the mood atmosphere created by subjects studied in groups, e.g., secobarbital (Nowlis and Nowlis, 1956; Sicé *et al.*, 1975), and alcohol (McClelland *et al.*, 1972; Pliner and Cappell, 1974), marihuana cannot be considered unique in apparently increasing a person's susceptibility to the moods of others. It remains for future research to determine whether or not this susceptibility positively reinforces the use of marihuana.

4. THE "AMOTIVATIONAL" SYNDROME

Among the effects ascribed to marihuana use are apathy, lethargy, diminished drive and ambition, decreased productivity and goal-directedness, and indolence. It has been repeatedly argued that chronic marihuana use produces an "amotivational" syndrome which parallels a preoccupation with drug use (Mayor's Committee, 1944; Williams *et al.*, 1946; McGlothlin and West, 1968; Scher, 1970; Kornhaber, 1971; Kolansky and Moore, 1972; National Commission on Marihuana and Drug Abuse, 1972).

A critical examination of data often interpreted to support the amotivational syndrome hypothesis reveals that the evidence is not compelling. Moreover, systematic diagnostic criteria for establishing the presence or absence of an amotivational syndrome have not been developed (cf. Halikas, 1974). Early studies of chronic effects of marihuana in man (Mayor's Committee, 1944; Williams *et al.*, 1946) are difficult to interpret for two reasons. First, there was no method available to determine the potency of marihuana cigarettes and consequently it was impossible to specify dose-effect relationships. Secondly, behavioral data were derived entirely from qualitative observations by the investigators without independent, objective measures. More recent clinical studies of marihuana effects have often involved subjects with psychiatric problems who are not representative of average marihuana users. Consequently, apparent motivational impairments may reflect problems unrelated to marihuana use (cf. Kolansky and Moore, 1971). In a college-age population, an amotivational syndrome appears synonymous with clinical depression (Kupfer *et al.*, 1973; Halikas, 1974). Large population surveys indicate that marihuana users do not characteristically have psychiatric problems and are relatively "normal"

(Haines and Green, 1970; Kupfer *et al.*, 1973: Robbins and Tanck, 1973; Marcus *et al.*, 1974).

One persistent problem in evaluating the psychopharmacological effects of marihuana, or of any other psychoactive drug, is the uncritical use of hypothetical constructs which cannot be directly measured. For example, motivation cannot be directly observed and can be only inferred from some behavior. Ideally, an examination of the purported amotivational properties of marihuana would require objective observation of unrestricted work for a preferred reinforcer in the presence and absence of a range of marihuana doses. Motivation could then be operationally defined by the number of points earned and the total time spent in operant work.

A second methodological problem in studies of drug effects is that of providing an adequate reinforcer so that variations in operant work can be related to the effect of the drug on performance, rather than to the subject's lack of interest in the reinforcer. Most efforts to study the effects of alcohol on some performance measure in the drinking alcoholic have been confounded by the fact that reinforcers other than alcohol have not been adequate to inspire or maintain performance (cf. Mello, 1973, for discussion). The relative indifference of alcohol addicts to working for reinforcers other than alcohol (e.g., money, cigarettes) has been amply documented (Mello *et al.*, 1968; Mello and Mendelson, 1972).

Although several animal species have been reported to become "sluggish," "drowsy," "cataleptic," or simply "depressed" after Δ^9–THC administration (Grunfeld and Edery, 1969; Scheckel *et al.*, 1969; Black *et al.*, 1970; Dewey *et al.*, 1970; Frankenheim *et al.*, 1971), the doses administered were often high enough to produce ataxia (up to 18 mg/kg). Once behavioral tolerance developed, doses as high as 25 mg/kg failed to produce a comparable depressant effect.

Two studies have yielded information on the effects of chronic marihuana use in man on "motivation" as assessed by operant work, in the absence of any other drug use (Mendelson *et al.*, 1974, 1976). Data obtained on normal subjects did not support the concept of an amotivational syndrome. In one study (Mendelson *et al.*, 1974), subjects worked on a fixed-ratio (FR) schedule in which every 6,000 points earned could be exchanged for one marihuana cigarette or 50 cents. A daily limit of 60,000 points ($10.00) was established which required about five hours of work to be achieved. Subjects consistently earned the maximal number of points available and showed no evidence of a marihuana-induced impairment in work and/or motivation. However, conclusions drawn from the study are limited by the fact that subjects were not allowed to work for as long as they wished, or for as much as they could possibly earn. The arbitrary limit on daily earnings may have been too low to be sensitive to any marihuana dose-related effects.

Mendelson and his associates (1976) also examined marihuana self-administration patterns and compared the effects of chronic marihuana use on an objective measure of motivation (unrestricted operant work), under controlled research ward conditions. Operant work for marihuana cigarettes or for money, and the effects of marihuana smoking on behavior, were examined in 12 casual and 15 heavy male marihuana users. These volunteers were studied in groups of four on a clinical research ward and each subject served as his own control. A 5-day baseline period was followed by a 21-day period of marihuana availability and a 5-day postmarihuana control period. Subjects could earn 50 cents or one marihuana cigarette weighing one gram by 30 min of sustained performance on a simple operant task. All casual and most heavy users gradually increased marihuana smoking over the period of drug administration. The heavy users smoked more (4.3–6 cigarettes/day) than the casual users (2–3/day). Both groups worked between two and five times as many hours per day as was necessary to earn the number of cigarettes smoked. Consequently, subjects earned and saved far more money than was spent for marihuana. The heaviest smokers worked between 6.7 and 14.4 hours every day. Periods of maximal work coincided with periods of maximal smoking, i.e., between 4 p.m. and 12 midnight each day. Marihuana use had a delayed effect on points earned the following day in that the subjects showed a dose-related decrement in operant work output. In the heavy user group, operant performance was sharply decreased 24 hr after three cigarettes/day were smoked, but little additional decrement was observed when the consumption was as high as eight cigarettes daily. Performance decreased further on the few occasions when more than eight cigarettes were smoked. In the casual user group, a decrease in performance was observed 24 hr after the smoking of one marihuana cigarette. An additional decrease was observed when three or more cigarettes per day were consumed. No subject completely stopped operant work even when he smoked 10 or more marihuana cigarettes per day.

Although caution should be exercised in interpreting and generalizing from these results, the data suggest that when tolerant individuals smoke approximately three marihuana cigarettes, they can sustain work for money as well as for drug. Subjects tended to smoke far more during the study than they generally did off the ward. Consequently, moderate use (three cigarettes) may not significantly interfere with normal work performance. This interpretation is consistent with data from objective studies of social marihuana use and work patterns in Greece and Jamaica. Findings indicate that chronic marihuana use may not significantly affect work output in natural, uncontrolled settings (cf. National Commission on Marihuana and Drug Abuse, 1972; Weiss, 1972; Rubin and Comitas, 1975; Stefanis *et al.*, 1977). These results are concordant with findings that subjects with a past history of casual and heavy marihuana use showed no dose-related decrement in operant work for money or marihuana reinforcement when they worked on an FR schedule (Mendelson *et al.*, 1974). These data suggest that motivation may be as much a function of situational variables as of direct drug influence. It is evident that the type of task, its reinforcing consequences, the smoking and work setting and the presence or absence of reinforcement limits all exert critical influences on behavior.

Miles *et al.* (1974) reported that the efficiency (time to complete a unit) of assembling a wooden stool improved steadily over the course of chronic marihuana (and alcohol) use in five subjects under controlled research ward conditions. However, subjects did work fewer than the prescribed 7½ hr/day for 5 days/week, and the number of stools completed did decrease. Miles' subjects smoked approximately 7 to 70 mg of THC per day over 42 days (calculated from published data).

Miles' subjects also failed to show the lack of concern for material rewards commonly associated with an amotivational syndrome and negotiated two pay increases during the period of drug availability. Since these subjects could use both marihuana and alcohol and since the use of these substances showed a "low but consistent correlation" (Miles *et al.*, 1974), it is impossible to determine whether these data reflect primarily the effects of marihuana or the combined (and perhaps facilitatory) effects of marihuana plus alcohol.

Operant data obtained from casual and heavy marihuana users differ strikingly from operant data obtained from subjects physically dependent on alcohol. There was a dramatic dissociation between periods of working for alcohol on a comparable button-pressing manipulandum and periods of alcohol consumption (Mello and Mendelson, 1972). Despite the simplicity of the operant task, alcoholic subjects abstained from drinking while working, even to the point of experiencing uncomfortable partial withdrawal signs and symptoms, until they had earned enough points to support a 2- or 3-day drinking spree. This pattern of alternate periods of working and drinking was then repeated over the 60-day period when alcohol was available (Mello and Mendelson, 1972).

The difference in operant work patterns of alcohol addicts and marihuana users is dramatic since the 1,000 responses required to earn one ounce of alcohol could be emitted in only 5 to 10 min (FR 1,000), whereas 30 min was required to earn 1,800 points exchangeable for a single marihuana cigarette on a fixed-interval (FI) 1-second schedule.

The utility of the term *motivation* to describe certain aspects of human behavior has been questioned. Even the use of objective rather than traditional subjective measures to study the motivational effects of psychopharmacological agents cannot obviate the ambiguities inherent in this construct. The problems involved in the definition of motivation are several. In order to infer motivation or amotivation from some measure of work behavior, the adequacy of the presumed reinforcer to maintain work behavior must be clearly demonstrated.

5. MARIHUANA AND SHORT-TERM MEMORY

One of the most frequently cited effects of marihuana is its apparent interference with short-term memory. Early attempts to document this effect with controlled research led to inconsistent results. Some investigators found such an effect (Melges *et al.*, 1970a and b; Tinklenberg *et al.*, 1970; Drew *et al.*, 1972; Miller *et al.*, 1972; Pearl *et al.*, 1973) and others did not (Jones and Stone, 1970; Waskow *et al.*, 1970; Tinklenberg *et al.*, 1972; Bowman and Pihl, 1973). The inconsistency was attributed to variations in set and setting and to different measurement procedures employed from study to study. However, recent studies in this area were based on a systematic analysis of the processes involved in short-term memory, and these studies have yielded more consistent results. In brief, these latter studies suggest that it is the information acquisition and storage phases of short-term memory that are most susceptible to marihuana effects, the phases that are heavily dependent on attention (Abel, 1970, 1971a and b; Dornbush *et al.*, 1971; Dittrich *et al.*, 1973).

The suggestion that marihuana-related deficits in short-term memory are mediated through the drug's interference with attentional processes appears to conflict with the results of studies which indicate that marihuana does not directly interfere with the ability to sustain attention (Weil *et al.*, 1968; Meyer *et al.*, 1971; Kopell *et al.*, 1972; Low *et al.*, 1973; Rafaelsen *et al.*, 1973; Vachon *et al.*, 1974;). The resolution of this apparent conflict may lie in the findings of still other studies which indicate that motivated subjects can volitionally control some drug effects well enough to perform adequately on experimental tasks (Tart, 1970; Tinklenberg *et al.*, 1970; Cappell and Pliner, 1973; Rossi and O'Brien, 1974; Casswell, 1975).

One hypothesis that may be drawn from an integration of the findings from these three areas of marihuana research is that subjects' marihuana-related performance on a short-term memory task will vary according to the degree of attention they devote to experimental tasks. Rossi *et al.* (1977) studied 27 adult male marihuana smokers who volunteered to participate in a hospital research ward study for a 31-day period. Following five days of baseline acclimatization, subjects could purchase and smoke marihuana cigarettes on a free choice basis for a period of 21 consecutive days. The marihuana smoking period was followed by a concluding five-day baseline. Measurements of simple reaction time, choice reaction time, and short-term memory were carried out during the entire study. Analysis of variance revealed no statistically significant differences between control and marihuana performance; however, a correlational analysis showed that individual subject performances on all three tasks were significantly correlated from test session to test session during control conditions but not during marihuana smoking conditions. The failure to find significant differences in the analysis of variance appeared to be at least partially related to large daily fluctuations in marihuana-related performance. Indeed, large variations in marihuana-related assessments have been reported so frequently (Clark *et al.*, 1970; Waskow *et al.*, 1970; Grinspoon, 1971; Pearl *et al.*, 1973; Rafaelsen *et al.*, 1973; Casswell, 1975) that inconsistent performance may be one of the few reliable effects attributable to marihuana use.

6. MARIHUANA EFFECTS ON INTERPERSONAL BEHAVIOR

A number of questions have been raised about the interpersonal effects of marihuana, particularly with respect to personality alterations, social functioning, and antisocial behavior. One pattern of behavioral change attributed to chronic marihuana use has been summarized under the concept of "amotivational syndrome" (McGlothlin and West, 1968), as discussed in Section 4. Impaired social functioning has also been attributed to the acute effects of marihuana. Brubaker (1973) has suggested that an individual cannot participate normally in expected societal roles while under the influence of cannabis.

The alleged negative consequences of marihuana have not always been attributed to the direct pharmacological action of the drug, however. Several writers (Grinspoon, 1971; McGlothlin, 1972; Thurlow, 1973) have noted that the appearance of "amotivation" may arise from predisposing personality problems, from prior or concomitant use of other drugs, or from gradual socialization into a drug-using subculture which de-emphasizes conventional achievement. These observations attest to the need for controlled research in which the pharmacological effect of marihuana on social functioning is differentiated from sociological and personal factors. Further, there is a need to study users differing in prior experience with the drug in order to evaluate the role of tolerance to the behavioral effects. If tolerance does develop to the changes in social response induced by marihuana, experienced users during intoxication should be indistinguishable in their performance from nonintoxicated control subjects.

Several researchers have studied social reactions to marihuana in controlled settings. The major features of these studies are outlined in Table 2, which summarizes information on subjects, marihuana dosage, experimental procedures, and findings.

Weil and Zinberg (1969) found that marihuana exerts a subtle disruptive influence on speech, possibly by interfering with short-term memory. Paul and Carson (1973) reported that focused verbal communication is impaired during intoxication. Galanter *et al.* (1974) studied intoxicated subjects during and after sensitivity group meetings. Although subjects reported feelings of detachment under marihuana, no consistent changes were noted in affect, insight, or group cohesiveness. In an intensive multidisciplinary investigation of casual and heavy users, Babor *et al.* (1974a and b) studied effects of marihuana on verbal interaction and problem solving. An inverse relationship was found between the level of intoxication and the amount of group interaction in discussion-group situations. The quality of communication was also affected, subjects becoming less task-oriented and more positive in their verbal interaction. In problem-solving groups, intoxicated subjects were less likely to assume a role of leadership. The observed effects tended to be less pronounced in the heavy users, suggesting the existence of tolerance to these effects on behavior.

Babor and his colleagues (1978) studied four-person groups of moderate and heavy marihuana users in a group discussion situation during marihuana intoxication. The amounts of participation and role behavior were compared with nonintoxicated baseline performance and with those of a no-drug control group. During intoxication, moderate users were less task-oriented and participated less in group discussion. The lack of any social effect on heavy users suggested the existence of tolerance.

The results obtained by Babor *et al.* (1978) offer partial support for the hypothesis that marihuana has predictable effects on interpersonal behavior in the areas of group participation and task orientation, and that tolerance to these effects may develop in heavy users. The findings are also consistent with the results of previous research (Babor *et al.*, 1974b) in which decrements in amount of interaction and task-oriented content were directly related to marihuana intoxication. However, the results fail to confirm the prediction that the role dimensions of

TABLE 2

Experimental Studies of Social Reactions to Marihuana

Subjects	Dose	Assessments	Findings	Limitations	Reference
10 casual users; 10 heavy users; all males	Self-selected; 1 g, 2% THC cigarettes	Number, quality of questions, and suggestions in "20 questions" task	Fewer questions proposed; no change in overall performance	Variable dose; no control group	Babor *et al.*, 1974a
10 casual users; 10 heavy users; all males	Self-selected; 1 g, 2% THC cigarettes	Amount, quality of verbal interaction in group discussion task	Less interaction; greater percent positive content; smaller percent task content	Variable dose; no control group	Babor *et al.*, 1974b
9 males; 9 females; 2–4 yr marihuana use	470 mg cigarette; 7.5 mg THC; placebo	Self-reports of group atmosphere, cohesiveness, subjective effect, normative behavior during sensitivity groups	No change in feelings of cohesiveness, normative behavior. Subjects felt less involved; saw others as happier, less involved	No empirical observations of behavior	Galanter *et al.*, 1974
30 experienced male users	Cigarette: 7 mg THC/kg	Mood questionnaire; video-taped dyadic interaction	Memory loss, mind wandering, mood fluctuation, interruptions	Methods inadequately described; no placebo or controls	Paul and Carson, 1973
9 male chronic users	Placebo and 2 g, 9% THC cigarettes	Verbal samples before and 50 min after	Highly variable; "subtle" changes in speech	Neutral setting; artificial situation	Weil and Zinberg, 1969

dominance and friendliness would also be affected by marihuana intoxication.

The findings of Babor *et al.* (1978) point to two conclusions concerning the influence of marihuana on social behavior. First, marihuana intoxication precipitates social withdrawal in moderate users. In formal discussion groups, the intoxicated individual also changes his social role in that he gives less attention to a specific task. Second, the effects of marihuana on behaviors such as verbal interaction may be mitigated by tolerance, since the tendency to withdraw was found to be nonexistent in heavy users.

Several explanations may be proposed to account for the changes in participation and task-orientation during intoxication. Numerous studies have shown a relation between marihuana use and impaired cognitive performance (Clark *et al.*, 1970; Melges *et al.*, 1970a and b). Melges *et al.* (1970a and b) have summarized these effects under the term "temporal disintegration," which is defined as difficulty in retaining, coordinating, and indexing goal-related information. For users who have not yet developed tolerance to these effects, task-oriented verbal interaction may be too cognitively demanding.

A second explanation would relate the observed changes in social behavior to marihuana-induced changes in motivation. If the so-called amotivational syndrome is a direct result of the pharmacological effects of marihuana, then it would be expected that goal-directed interaction would be reduced. However, dominance behavior would also be expected to diminish, a prediction which received only limited support.

A third hypothesis would include both cognitive and motivational factors and the way in which these factors are related to the subjective experience. This interpretation is consistent with subjective reports of detachment given by subjects studied by Galanter *et al.* (1974), and with the hypothesis that drug-induced states of consciousness represent a re-organization of mental functioning (Tart, 1971; Ornstein, 1972). Particularly in the case of moderate users, there appears to be a shift from a social, verbal, external focus of attention to a more internal, receptive, contemplative orientation.

7. CONCLUSIONS AND IMPLICATIONS

Relatively little new information on the behavioral and biological aspects of *chronic cannabis use* has appeared since the publication of conference proceedings describing comprehensive studies in this area, in the *Annals of the New York Academy of Sciences* edited by Dornbush *et* *al.* (1976). These data suggested that marihuana use produced a mild to moderate degree of intoxication with no long-term residual derangements of brain function or behavior. However, even in the absence of well-documented marihuana-induced CNS problems in both epidemiological studies and experimental studies of daily administration, most participants in this conference agreed that more data were necessary before any good predictions about potential health hazards associated with marihuana use could be formulated. It is surprising, therefore, that so few new data have been forthcoming during the past five years, since many more questions were raised than answered at the conference and it was anticipated that these questions would stimulate further research. In fact, no major studies including carefully controlled and monitored inpatient clinical investigation of chronic cannabis effects have been reported during the past five years. There also appear to be no studies of this type currently in progress. With respect to long-term population surveys, no data have been forthcoming concerning new CNS health hazards as a consequence of chronic marihuana use.

Given the relative dearth of new information, we are forced to rely upon a limited number of experimental and epidemiological studies of chronic cannabis use which have many acknowledged shortcomings. It is possible to interpret the situation in two ways. On the optimistic side, given the very widespread use of marihuana in contemporary society, it is reassuring to note that a large number of case reports of marihuana-related derangements in brain function and behavior have not appeared in the biomedical literature. It may be assumed that if chronic heavy marihuana use among some subpopulations were associated with enhanced risks for some specific type of neural or behavioral problem, this association would have been identified and reported.

A more pessimistic view is that the relative lack of more intensive experimental and epidemiological research is impeding discovery of significant marihuana-related health hazards, particularly those associated with brain function and behavior. It may be necessary for considerable time to elapse for detection of marihuana-related disorders. This situation would be analogous to the lack of a recognized relationship between cigarette smoking and carcinoma of the lung and cardiovascular disease until after a very large number of individuals had smoked cigarettes for long periods of time. Unfortunately, several decades may pass before we are aware of some potentially dangerous and perhaps lethal concomitants of chronic marihuana use.

Many investigators have commented that research which has been carried out to date was conducted with dose-time paradigms which may no longer be relevant to contemporary marihuana use. The health hazards associated with the use of any psychoactive compound, including opiates, alcohol, and marihuana, must take into account evanescent changes in dosage patterns and frequency of substance use as well as the potency and availability of the drug. At the present time, we have very limited information about potential health hazards associated with relatively low dose chronic marihuana use. These data taken together provoke no great alarm. What is alarming, however, is that the meager data we now possess are not sufficient for either good scientific predictions or health policy formulation. At this juncture, we should honestly admit that we do not have sufficient information to make good predictions about potential health hazards to the CNS associated with chronic marihuana use. This statement may be viewed as self-serving by individuals outside of the biomedical research community and possibly as scientific evasion by policy-making groups who either favor or disapprove of attempts to legalize marihuana use. Nevertheless, we should urge research designed to increase acquisition of data which may precede and perhaps preclude a serendipitous discovery of possible adverse outcome of chronic marihuana use.

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Long-Term Effects of Cannabis on Cerebral Function: A Review of the Clinical and Experimental Literature

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1. INTRODUCTION

Although the acute behavioral effects of cannabis have been recognized for many centuries (Abel, 1980), it is mainly within the last one hundred and thirty years that a few clinical descriptions of the effects of long-term heavy cannabis use have appeared in the medical literature.

Over the past fifteen years, coinciding with the dramatic increase in cannabis use in Western countries, there has been a steady accumulation of clinical and experimental data pertaining to the question of cannabis-induced cerebral deficits. This evidence has evoked a great deal of controversy among scientists, politicians, and the general public. There is no doubt that real and substantial inconsistencies in the literature have been magnified by those who tend to cite selected pieces of evidence in support of their own ideological beliefs.

In this review, the information pertaining to possible cannabis-induced organic brain damage will be summarized. This evidence consists of clinical descriptions and case reports, quantitative estimations of neurological and psychological function, and experimental studies using animal models. Conclusions will be made according to the same criteria that have been used to evaluate the toxicity of other drugs such as alcohol

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and amphetamines, and comparisons will be made with these drugs where possible.

For the purposes of this discussion, heavy use has been defined as consumption of cannabis products at least daily; moderate use, one to six times per week; and light use, less than once per week.

2. CLINICAL STUDIES

Clinical Observations

Early Observations

A perusal of the early clinical literature is both entertaining and informative. In one of the first accounts of cannabis effects (Wise, 1852), the superintendent of the Dacca Insane Asylum in Bengal writes:

> *But it is also well known that a constant, or large consumption of it* [*gunja*], *makes the person unfit for business, and, if continued, produces insanity . . . . It, by use, weakens the animal passion, memory, power of voluntary control of the thoughts, or fixing the attention.*

From Africa, India, the Middle East, and other countries where heavy and prolonged cannabis consumption was prevalent among the males of the lower social classes, many comparable descriptions were published over the next hundred years. A list of references selected to illustrate the geographical origins and nature of these observations appears in Table 1. The authors, with a greater or lesser degree of precision, described a general picture of physical deterioration accompanied by symptoms of CNS dysfunction such as apathy and deficits in memory, attention, and cognition. A typical example is taken from the report of Guichard (1919), a physician who studied Moroccan users of up to 100 "pipes" of hashish per day. The typical Moroccan hashish pipe is very small and the hashish is ordinarily co-combusted with tobacco which fills most of the bowl. The amount of hashish per pipe might be about 100–200 mg, since the maximum consumption of kif is about 18 g/day (Sigg, 1963).

> *Cette déchéance intellectuelle se double dans la plupart des cas d'une déchéance physique profonde, et les fumeurs invétérés acquierent un habitus et un facies qui les font facilement reconnaître. Ces individus ont l'air hébété, farouche, la parole lente, la compréhension difficile. Leur visage est sans expression, les paupières et les lèvres tombantes, le teint plombé, les conjunctives jaunes, la marche et les mouvements*

> *ralentis et incertains. Ils répondent difficilement ou pas du tout aux questions qu'on leur pose.*
>
> [*This intellectual deterioration in the majority of cases is accompanied by a profound physical deterioration, and the inveterate smokers acquire a physical habitus and a facies that make them easy to recognize. These individuals have a dull, unsociable air about them; they speak slowly and comprehend with difficulty. Their face is without expression, their eyelids and lips droop, their color is grey, their conjunctivae yellow, their gait and movements slow and uncertain. They answer questions with difficulty or not at all.*]

The various descriptions cited are remarkably similar despite the time span of more than one hundred years, and the wide range of countries surveyed. This consistency is made more noteworthy by the fact that concomitant use of drugs other than cannabis would have varied considerably from country to country.

It is nonetheless extremely difficult to draw definite conclusions about the role of cannabis from these descriptions. Most are statements of conclusions, supported by few or no case data. There is a lack of precise information on the subjects themselves and on the dosage, extent of cannabis exposure, and the prevalence of these findings among the population of users. However, it seems likely that most of these cases occurred in inveterate users of large amounts such as several grams of hashish a day. Although an attempt has been made to include only those papers in which "dementia" or more specific features of organic brain dysfunction are discussed, the lack of standardized terminology during that period often makes the distinction between organic disorders and psychosis impossible. This point is illustrated by the report of Ewens (1904) who briefly described 95 cases of hemp-induced insanity. In that paper, enough details are provided to enable one to conclude that the six "demented" patients were almost certainly suffering from a chronic psychosis rather than an organic brain disorder.

In most reports, there is no distinction between acute and/or chronic drug effects and residual, possibly permanent, effects that persist after discontinuation of drug use. An exception was Hesnard (1912), a French psychiatrist who observed chronic hashish users in the Middle East and suggested that the chronic effects on intellectual function may not always be reversible.

> *Le fumeur d'habitude est toujours abruti, intellectuellement et moralement . . . . L'aspect général est celui de la déchéance physique, de la sénilité précoce . . . . Même à ce*

TABLE 1

Selected Examples of Early Descriptions and Case Reports

Country of Origin	Extent and Duration of Use	Observations During Chronic Intoxication	Observations During Recovery	Reference
Bengal	chronic	—deficits in attention, memory	—about 33% recover	Wise, 1852
Guyana		—dementia		Ireland, 1893
Egypt		—memory impairment, apathy —no motor or sensory symptoms —may be end result of psychosis		Warnock, 1903
Surinam		—progressive dementia	—not reversible	Scholtens, 1905
Crete Turkey Syria	10–40 pipes/day	—intellectual and moral deterioration —dementia	—physical health recovered —intellectual impairment may never fully recover	Hesnard, 1912
Morocco	40–100 pipes/day	—slow speech, poor comprehension, dementia, irritability		Guichard, 1919
Tunisia		—chronic mental confusion —dementia		Perrussel, 1925
India	heavy and prolonged	—a few cases of chronic hemp mania progress to dementia	—40% recover from “chronic disorders”	Dhunjibhoy, 1928

Turkey	chronic users	—slow cerebration, memory impairment, impaired attention, apathy	Kerim, 1930
India	chronic	—dementia observed rarely (3% of 600 cases of hemp insanity) —“progressive weakening of all faculties of brain”	Chopra *et al.*, 1942
North Africa	heavy for many years	—“mental epilepsy,” confusion, impaired memory, “intellectual torpor”	Bouquet, 1951
Egypt	long-term use	—“severe disturbances of the intellectual faculties”	Abdulla, 1953

> *degré, quand les viscères ne sont pas profondément altérés, la cure de désintoxication est possible. Mais l'intelligence reste obscurcie très longtemps et le malade ne reprend jamais son activité psychique antérieure.*
>
> [*The habitual smoker is always stupefied, intellectually and morally . . . . The general look is one of physical deterioration, of premature senility . . . . Even at this point, if the viscera are not seriously damaged, successful detoxication is possible. But the intellect remains clouded for a very long time and the patient never resumes his former mental activity.*]

Recent Observations

Selected examples of more recent clinical observations spanning the last fifteen years have been listed in Table 2. These reports generally have more complete descriptions of individual cases. The more extensive information on drug exposure suggests that CNS dysfunction is most often associated with heavy (at least daily) use for more than one year. The interpretation of these descriptions is also facilitated by standardized and precise terminology. Thus a distinction usually can be made between CNS deficits and psychosis, even though both disorders may be described in the same paper.

The observations of chronic intoxication are illustrated by the following excerpts:

> *These patients consistently showed very poor social judgment, poor attention span, poor concentration, confusion, anxiety, depression, apathy, passivity, indifference and often slowed and slurred speech* (Kolansky and Moore, 1971);

. . .

> *. . . the underlying brain syndrome* [*was*] *characterized in his case by slight but definite memory deficits, impaired intellectual functioning and impaired judgement. He let it be known that even when not under the acute influence of cannabis, he finds: 'There are things I should remember but can't . . .'* (case #5 from Hart, 1976);

. . .

> *All 110 patients exhibited a personality disturbance which prompted psychiatric consultation at some point during their*

> *period of high-dose hashish consumption. Despite variation in overall symptomatology, all displayed symptoms of chronic intoxication similar to those found in individuals dependent on depressant-hypnotic drugs. Major manifestations were apathy, dullness, and lethargy with mild-to-severe impairment of judgment, concentration and memory. Intermittent episodes of confusion and inability to calculate occurred with high levels of chronic intoxication* (Tennant and Groesbeck, 1972).

Despite the more modern terminology, it is clear that these reports largely recapitulate what was described by the earlier clinicians. Thus the recent observations from Western countries, where widespread cannabis use is a relatively new phenomenon, broaden even further the time span and geographical range in which the same clinical impressions recur.

Modern clinicians have begun to distinguish more systematically between chronic intoxication and the residual effects of heavy drug use. It is apparent that although some patients appear to recover completely, others do not. Kolansky and Moore (1972) described a patient (case #13) who recovered:

> *Within two months of beginning the treatment she stopped marihuana smoking. Within three months there was a lessening of the confusion and poor attention span. At the end of nine months, the confusion, lack of concentration, poor attention span and inappropriate appearance had disappeared;*

and another (case #12) who did not:

> *. . . . he slowly withdrew from the cannabis habit. As he did so, his thinking became clearer and his memory improved; however, after six months he still had difficulty with immediate recall, often demonstrated by his forgetfulness and frequent loss of personal belongings . . . . One year after cessation of marihuana use, he demonstrated and complained of some difficulty in maintaining long periods of concentration and an inability to satisfactorily convert his thoughts into written or spoken words.*

Similarly Hart (1976) observed both recovery (case #7):

> *His cerebration, formerly so pitiful and sluggish, now [one-year post-drug] functioned well enough for him to dismiss . . . my role in his improvement;*

TABLE 2

Selected Examples of Recent Descriptions and Case Reports

Country of Origin	Type of Report	Extent/Duration of Use	Observations During Chronic Intoxication	Observations During Recovery	Reference
Morocco	S[1]	$\overset{c}{h}$/chronic	—memory loss, low intelligence		Christozov, 1965a and b
Morocco	D[2]	h/chronic	—perseveration, poor verbal expression, cognitive disruption		Vierth, 1967
France	S	habitual	—reduction of intellectual activity —mystical interests		Deniker *et al.*, 1970
U.S.A.	Q[3]	several years	—subjective complaints of cognitive inefficiency, impaired memory and judgment		Scher, 1970
U.S.A.	S	h	—speech showed signs of intellectual deterioration despite increased use of imagery and greater circumstantiality		Zinberg and Weil, 1970
Vietnam	CR[4]	"abuse"	—irritability, poor concentration, impaired verbal communication		Kaplan, 1971

U.S.A.	S	h/≥ 1 yr	—impaired attention span —poor concentration	—improvement seen 4–6 wk postdrug	Kornhaber, 1971
U.S.A.	S	m[b],h/1–6 yr	—impairment of memory, concentration, attention span and ability to organize thoughts	—a few cases had persistent memory and concentration deficits 8–10 mo postdrug	Kolansky and Moore, 1971, 1972
Thailand	CR	h/> 3 yr	—altered time sense, fixing on ideas, slowed mentation	—postdrug recovery "over next few days"	Kroll, 1975
U.S.A.	S	h	—poorer performance on cognitive tasks than expected from academic achievement		Barratt *et al.*, 1972
Canada	D	m,h/1–2 yr	—"fluctuating low grade high while not intoxicated" —lack of interests, cognitive impairment	—recovery after 2–3 drug-free weeks	Schwarz, 1972

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1. S = Series
2. D = Description
3. Q = Questionnaire
4. CR = Case Report

a. 1 = light use (< once/week)
b. m = moderate use (1–6/week)
c. h = heavy use (≥ once/day)

TABLE 2 (CONTINUED)

Country of Origin	Type of Report	Extent/Duration of Use	Observations During Chronic Intoxication	Observations During Recovery	Reference
West Germany	S	h/0.5–1 yr	—"mild to severe" impairment of memory, judgment and concentration	—66% recovered after 2–4 drug-free weeks —33% showed intermittent episodes of memory loss and confusion up to 9 mo postdrug	Tennant and Groesbeck, 1972
U.S.A.	Q	1^a,m,h	—memory less sharp in heavy users		Kupfer *et al.*, 1973
South Africa	S	m,h	—some intellectual impairment —attention disorders in 30% of heavy users —memory disorder in 8% of heavy users	—speculation of partial or complete recovery postdrug	Levin, 1974
Canada	Q		—impairment of concentration in 25% of sample		Negrete, 1974
Nepal	S	h/≥2 yr	—poor work performance, slow, limited interests —vague monotonous speech	—recovery within 4 mo of discontinuation	Sharma, 1975

Canada	D	m,h/4–6 wk	—impaired thought processes	—reversible during periods of light use	Campbell, 1976
U.S.A.	CR	m,h	—impairment of intellectual function, memory and judgment	one case had “detectable” deficits 18 mo postdrug	Hart, 1976

and residual effects (case #6):

> *After six months of abstinence, most of the organicity had cleared . . . .* [*Eighteen months later*] *there were still some detectable deficits in intellectual functioning, orientation, and memory.*

In the only prospective study to date, Tennant and Groesbeck (1972) observed nine American soldiers before, for 3 to 12 mo during and for 3 to 12 mo after periods of heavy (50 to 250 g/mo) hashish use:

> *After complete discontinuation of hashish abuse, memory, alertness, concentration and calculating ability returned to normal within two to four weeks in six of the nine patients . . .* [*The three heaviest users (in terms of dose or duration)*] *exhibited intermittent residual symptoms analogous to those of organic brain disease . . . . With passage of time these episodes* [*memory loss, confusion and inability to calculate and concentrate*] *became less severe and less frequent.*

The clinical observations, particularly those of Kolansky and Moore (1971, 1972), have evoked a great deal of discussion and criticism (Benson, 1971; Bennett, 1972; Kuhn, 1972; Rosenthal, 1972; Watts, 1973; Beuthin, 1975). However, it is interesting that while the critics have faulted the "experimental design" (i.e., the choice of subjects, the lack of suitable controls), and the conclusions and extrapolations based on the evidence, the observations themselves have been largely unchallenged. To criticize clinical reports of this kind on the basis of poor "experimental design" is, by definition, inappropriate since these studies are *not* experiments. Altman and Evenson (1973), in an attempt to replicate the Kolansky and Moore (1971, 1972) study, examined 158 male and female psychiatric patients. The authors identified 38 of these patients who demonstrated symptoms similar to those reported by Kolansky and Moore (1971) and who had a prior history of marihuana use. However, of the total group of patients greater numbers had begun beer drinking, sexual activities, driving or other normal adolescent activities than had begun marihuana use before the onset of treatment. Altman and Evenson therefore concluded that they could find no causal relationship between marihuana use and the onset of psychopathology. This is a *non sequitur* because they failed to state whether the symptoms of the marihuana users differed from those of nonusers. Therefore, a possible relationship between cannabis use and a particular set of symptoms could still have existed without having been recognized by these authors.

Clinical observations, while clearly playing an important and primary role in the identification of drug-related side-effects, do have inherent limitations of interpretability. Although they can suggest an association between the chronic use of cannabis and impairment of brain function, they do not provide effective separation of cannabis from other potentially contributing factors such as malnutrition, disease, pre-existing psychopathology, or the use of other drugs. In addition, by their retrospective nature, they can give no accurate indication of the frequency of the specific drug-induced effect in a given population of users. These clinical observations, consistent over time, location, and culture, therefore serve to raise the level of concern regarding the possibility of cannabis-induced cerebral deficits, but in themselves do not provide evidence of causality.

Quantitative Clinical Test Data

The CNS function of chronic cannabis users has also been studied by a variety of quantitative and semi-quantitative test methods. These measures are intended to be objective and are quantifiable without reference to clinical judgment or to data on the extent of drug use. In addition to serving as diagnostic tools, they can serve to clarify the relationship between the drug and various CNS processes.

Neuropathology

Although neuropsychological deficits are not directly related to the appearance of neurological symptoms, it has been recognized that with other agents, such as ethanol, cognitive impairment often occurs in conjunction with other signs of CNS malfunction such as oculomotor and reflex abnormalities and is frequently found in conjunction with degenerative changes such as cortical atrophy (Wilkinson and Carlen, 1980). For this reason, we have examined the clinical literature for evidence of significant cannabis-related neurological dysfunction or morphological alteration.

Studies in which a complete neurological examination has been performed on cannabis users are listed in Table 3. In all studies of nonintoxicated healthy subjects, either no neurological impairment was found, or minor abnormalities were reported in a small proportion of the subjects (Mayor's Committee on Marihuana, 1944; Grant *et al.*, 1973; Agarwal *et al.*, 1975; Rubin and Comitas, 1975; Bernstein *et al.*, 1976; Chopra and Jandu, 1976; Coggins *et al.*, 1976; Boulougouris *et al.*, 1977). However, in several of these studies, individuals with obvious psychological or physical damage were excluded *a priori*, and this would

TABLE 3

Studies of Clinical Neurology

Type of Study	Sex	Age (range or mean in years)	N	Description of Ss	Extent of Use	Duration of Use (range or mean in years)	Drug-Free Period (days)	Observation	Reference
S[1]	♂	15–60	600	mental patients	h[c]	?	?	—hyperreflexia	Chopra *et al.*, 1942
CS[2]	♂	21–45	40	prisoners	h	2–16	14–700	—no abnormalities	Mayor's Committee on Marihuana, 1944
S	♂	10–60	140	psychotics	h	0.5–21	?	—headaches (often during abstinence) —hyperreflexia in 46 Ss —hyporeflexia in 21 Ss	Christozov, 1965a and b
S	♂,♀	13–24	38	mental patients	m[b],h	1–6	?	—slurred speech] seen in —staggering gait] a "few"] Ss —hand tremors	Kolansky and Moore, 1971
CS	♂	23.5	29	medical students	1[a], m	4.0	?	—no abnormalities	Grant *et al.*, 1973

S	♂	<45	40		h	≥5	>0.3	—no abnormalities	Agarwal *et al.*, 1975
CS	♂	23–53	30		h	>7	2–3	—1 case "Jamaican neuropathy"	Rubin and Comitas, 1975
exp. admin.	♂	21–31	28	healthy Ss	m, h	5.5	5	—no abnormalities	Bernstein *et al.*, 1976
S	♂	17.2 19.1 29.7 48.5	89 72 58 56		h	2–27	"post-intoxication"	—no abnormalities reported	Chopra and Jandu, 1976
CS	♂	<50	84		h	>10	?	—no abnormalities	Coggins *et al.*, 1976
CS	♂	41.3	44		h	24.3	"non-intoxicated"	—minor abnormalities in 6 Ss incl. transitory vertigo, reduced grip strength, hyperreflexia, mild tremor of tongue, absent corneal reflex, impaired sense of vibration	Boulougouris *et al.*, 1977

1. S = Series
2. CS = Controlled Series

a. l = light use (< once/week)
b. m = moderate use (1–6/week)
c. h = heavy use (≥ once/day)

obviously reduce the likelihood of finding significant abnormality among the users. This point will be commented on later in this review. Psychiatric patients were more likely to display mild abnormalities such as altered tendon reflexes, tremor, ataxia, and headaches (Chopra *et al.*, 1942; Christozov, 1965a and b; Campbell *et al.*, 1971; Kolansky and Moore, 1971). Since the drug-free period was not stated in any of the latter studies, the patients may have been intoxicated at the time of examination.

One group (Coleman *et al.*, 1976) reported that 82% of a group of American heavy users exhibited ocular hyperphoria due to paresis of the fourth cranial nerve. The hyperphoria was associated with headaches, and did not disappear when marihuana use was discontinued. This finding has not been confirmed elsewhere. In addition, Spector (1974) reported significant but minor changes in vestibular function in a group of American moderate and heavy users as compared with a nonuser control group, but he stated that the clinical significance of these changes was unclear.

In summary, the available evidence suggests that gross changes in neurological function are relatively rare among heavy long-term cannabis users and are found most frequently among those who are defined as patients, i.e., who have sought treatment. As with any uncommon phenomenon, only carefully-designed epidemiological studies will provide an accurate estimate of the prevalence of these symptoms among various groups of chronic cannabis users. It is known, for example, that neuropathology of the type described by Courville (1955) is found in only a small proportion of chronic alcoholics. In one study of this type, Ashley *et al.* (1981) reported that peripheral neuritis was observed in only 6.7% of a population of 1,001 inpatient alcoholics who had consumed at least 80 g of ethanol per day for a mean of 20 yr. Therefore the relative rarity of these symptoms among cannabis users is not surprising, and cannot, at this point, be used as a basis for assertions about lack of toxicity.

Cerebral Atrophy

In 1971, Campbell *et al.* performed pneumoencephalographic examinations on a series of 13 heavy cannabis users. Most of these patients had gross neurological abnormalities and clinically evident behavioral changes, and many had histories of polydrug use, head injuries, and epilepsy. The claimed finding of cortical atrophy (reflected by alleged increases in the sizes of the lateral and third ventricles) in these patients was and continues to be widely publicized despite many justified and some unjustified criticisms of investigational technique and of the selection of user and control subjects (Bull, 1971; Brewer, 1972; Grinspoon, 1972; Susser, 1972).

More recent studies of small numbers of healthy cannabis users carried out by the less invasive techniques of echoencephalography (Boulougouris *et al.*, 1977) and computerized tomography (Co *et al.*, 1977; Kuehnle *et al.*, 1977), have failed to confirm the earlier observation of cortical atrophy. Cortical atrophy, therefore, does not appear to be a common finding even among heavy users who show normal neuropsychological status.

By contrast, chronic alcoholics of all ages tend to have larger cerebral ventricles and cortical sulci than nonalcoholics matched for age (Wilkinson and Carlen, 1981), even in the absence of detectable neuropsychopathology (Wilkinson and Carlen, 1980).

Only one author has described postmortem studies of the brains of cannabis users. In 1928, Dhunjibhoy reported no abnormal macroscopic findings in the brains of two heavy users suffering from "hemp insanity." Clearly, further postmortem examinations, particularly those using more selective techniques for demonstrating fine detail of cell structure and synaptic connections, are necessary to yield useful information on the presence or absence of cerebral atrophy, histopathology, and neurochemical changes in heavy users.

Electroencephalography

The electroencephalogram may be used in a variety of ways to yield useful information on brain function. Visual and computerized techniques have been used for assessment of the EEG obtained at rest or during sleep, and for analysis of the wave forms of the evoked response. While EEG abnormalities are not directly related to behavioral impairment, they do give some information on CNS dysfunction, gross pathology, arousal levels, and response to stimuli. In studies of chronic alcoholics, computer analysis of EEG recordings has revealed minor abnormalities in wave frequency and power which have been correlated with neurological and intellectual impairment (Wilkinson and Carlen, 1980).

EEG studies of volunteers acutely intoxicated with cannabis have revealed a more or less consistent pattern characterized by enhanced alpha activity, decreased beta activity, and a slowing of the mean frequency (Fink *et al.*, 1976). This pattern is not specific for cannabis, but is shared by many sedative drugs, as well as by spontaneous drowsiness in the absence of drugs. The EEG findings have been much more variable in cannabis users who were not intoxicated at the time of examination.

The majority of investigators (listed in Table 4) have concentrated on the visual observation of gross abnormalities such as abnormal wave forms or marked changes in dominant frequency (Christozov, 1965a and b; Miras, 1969; Deliyannakis *et al.*, 1970; Campbell *et al.*, 1971; Hall, 1972; Tennant and Groesbeck, 1972; Farini Duggan and Aust, 1976; Panayiotopoulos *et al.*, 1977; Wig and Varma, 1977). In most of these studies, the length of drug-free period preceding the examination was not specified. In the majority of these case reports and small series, any reported abnormalities tended to be minor, and there was no overall consistent pattern to the observed changes. Minor changes of dominant frequency are principally a reflection of variations in level of arousal, and cannot be considered indicative of brain dysfunction.

In one study (Hanley *et al.*, 1976), computer analysis of the EEG recordings of a small series of healthy nonintoxicated cannabis users and age-matched controls suggested dose-related subtle changes reflected by greater power in the delta band and phase angle differences in the alpha, beta, and theta bands. A phase angle difference indicates a change in the speed of electrical transmission relative to two recording sites.

Only one major examination of EEG sleep patterns in chronic users has been performed. Karacan *et al.* (1976) reported that there were no significant differences between the sleep patterns of healthy Costa Rican heavy users and those of a control group matched for age and other variables.

In one study of the visual evoked response in moderate users of cannabis, Richmon *et al.* (1974) observed that the amplitude of the response was higher or lower than that of a control group. Like EEG frequency, amplitude of sensory-evoked responses is most often a reflection of the level of arousal (Perrin *et al.*, 1974), and does not *per se* provide evidence about the functional integrity of the brain.

No consistent pattern of EEG abnormalities emerges from these studies. Additional work is clearly needed, using the sophisticated techniques employed by Hanley *et al.* (1976) that suggested the possibility of drug-induced abnormalities. Further computer-assisted studies of chronic users, performed both during, and for a sufficient period after, chronic intoxication, will assist in the separation of drug-induced effects from changes in the level of arousal, and of abnormalities caused by

TABLE 4

Clinical EEG Studies

Type of Study	Description of Ss	N	Extent of Use	Duration of Use (range in years)	Drug-Free Period (range in days)	Observations	Reference
S[1]	♂ psychotics	5	h[c]	0.5–21	?	—nonspecific disorders were correlated with personality changes —one was suggestive of cortical atrophy, one was epileptic	Christozov, 1965a and b
CR[2]	♂	2	h	25–35	0.75 and 28	—“slowing and increased fast activity” in both Ss	Miras, 1969
S	♂ soldiers age 20–25	27	l[a],m[b],h	1–9	1–30	—13 Ss normal —8 Ss increased theta —4 Ss high amplitude irregular theta	Deliyannakis *et al.*, 1970

1. S = Series
2. CR = Case Report
3. CS = Controlled Series

a. l = light use (< once/week)
b. m = moderate use (1–6/week)
c. h = heavy use (≥ once/day)

TABLE 4 (CONTINUED)

Type of Study	Description of Ss	N	Extent of Use	Duration of Use (range in years)	Drug-Free Period (range in days)	Observations	Reference
CS[3]	♂, ♀ age 16–22	22	l,h		2–60	—10 of 11 psychotic Ss—“abnormal” EEG —8 of 11 nonpsychotic Ss—“abnormal” EEG	Campbell, 1971
S	♂ age 15–65	8	h	1–40	“non-intoxicated”	—lack of synchrony between hemispheres —bursts of high voltage slow waves	Hall, 1972
S	♂ age 19–20	3	h	0.5–1	during recovery	—no abnormalities	Tennant and Groesbeck, 1972
CS	students	9	m,h	>1	1	—higher or lower percentage of alpha component —higher or lower amplitude of visual evoked response	Richmon *et al.*, 1974
CR	♂, ♀ age 20	2		1–3	?	—no abnormalities	Farini Duggan and Aust, 1976
S	♂ age 21–35	18	m,h		“non-intoxicated”	—greater power in delta band —phase angle differences in alpha, beta, and theta bands	Hanley *et al.*, 1976

CS	♂ age <50	39	h	10–27	cannabis consumed during day	—no major alterations in EEG sleep patterns —wave forms recorded but unreported	Karacan *et al.*, 1976
CS	♂ mean age 41	40	h	mean 24	"non-intoxicated"	—waves of users tended to have higher amplitude —number of abnormal EEGs similar to that of control group —no consistent pattern of abnormalities observed	Panayiotopoulos *et al.*, 1977
CS	♂ age 18–37	23	h	⩾5	0.5	—no abnormalities	Wig and Varma, 1977

chronic intoxication from those associated with withdrawal of drug and those which may be residual.

Clinical Studies of Residual Neuropsychological Impairment

Motivated by the case report data suggestive of cannabis-related deficits in memory, attention, perception, and comprehension, several investigators have attempted to distinguish nonintoxicated cannabis users from matched groups of nonusers by means of psychometric tests designed for the quantitative assessment of these functions. These studies (listed in Table 5) show considerable variation in subject selection, extent of cannabis exposure, test batteries used, and results obtained.

Subject Selection

The user group was usually chosen to be representative of the cannabis-consuming population in the country where the study was conducted. With the exception of the Mayor's Committee Study in 1944, the North American subjects were young, healthy, and relatively affluent college students, whereas the users in Jamaica, India, Egypt, Costa Rica, and Greece tended to be older, more poorly educated, and of lower socioeconomic status. In only one study (Soueif, 1971, 1975, 1976) did the number of users exceed 50. Controls were generally healthy nonusers who were matched *post hoc* for such variables as age, education, race, socioeconomic status, and alcohol use.

Drug Exposure

As well as being older, the Jamaican, Indian, Egyptian, Costa Rican, and Greek subjects had a much more extensive history of drug use than the North American subjects in terms of both duration of use and stated dose. Because of local variations in potency of cannabis and smoking techniques, actual doses of THC have been difficult to estimate. In future, estimations of peak blood levels of THC after smoking might provide more useful information than a calculation of the estimated number of grams of leaf material consumed per day (Petersen, 1979).

In some countries, it was also difficult to locate nonusing controls suitable for matching; it is suspected that in at least one study (Rubin and Comitas, 1975) most of the controls had drunk bhang occasionally for medicinal purposes.

Drug-Free Period

Again in these studies, virtually no attempt was made to separate the effects of chronic intoxication from manifestations of a possible abstinence syndrome or from impairment that could persist for long periods after the termination of drug administration. Where the drug-

TABLE 5

Clinical Studies of Residual Impairment

Location	Description of Ss	Age (range or mean in years)	N	Extent/Duration of Use (range or mean in years)	Minimum Drug-Free Period	Test Battery	Performance of Users	Reference
U.S.A.	♂ prisoners	21–45	38	h/≥1	14-700 days	—Bellevue Adult Intelligence Test	—no difference when matched for race	Mayor's Committee on Marihuana, 1944
U.S.A.	high school students	~14–17	?	m[b],h[c]/"chronic"	?	—embedded figures test	—no significant differences, however users poorer on first exposure to new level of problem difficulty	Barratt *et al.*, 1972
U.S.A.	students ♂, ♀			"casual" "frequent"	?	—Otis Quick-Scoring Mental Ability Test —Witkin's Group Embedded Figures Test	—no consistent relationship between users and nonusers	Cohen, 1972

a. l = light use (< once/week)
b. m = moderate use (1–6/week)
c. h = heavy use (≥ once/day)

TABLE 5 (CONTINUED)

Location	Description of Ss	Age (range or mean in years)	N	Extent/Duration of Use (range or mean in years)	Minimum Drug-Free Period	Test Battery	Performance of Users	Reference
U.S.A.	students ♂, ♀	~18	26	h/>0.5	"non-intoxicated"	—verbal and numerical memory	—users significantly poorer on verbal memory (recall and acquisition)	Entin and Goldzung, 1973
U.S.A.	medical students ♂	23.5	29	l[a],m/4.0	?	—Halstead-Reitan Battery	—users significantly poorer on localization subtest of Tactual Performance	Grant *et al.*, 1973
Canada	students ♂	22.0	11	m/≥3	?	—field dependence, cognitive function	—users had no impairment of cognitive function	Weckowicz and Janssen, 1973
Canada	students ♂	23.0	24	h/≥3	?	—field dependence and cognitive function and style, memory	—users outperformed controls on tests of cognitive function, originality and attention	Weckowicz *et al.*, 1977

U.S.A.	students ♂	20–25	56	l,m/1–4	?	—Halstead-Reitan Battery and other tests of perception, cognition, and psychomotor performance	—users who also used LSD were significantly poorer on Trails A and B	Culver and King, 1974
U.S.A.	students	18–22	9	m,h/≥1	1 day	—time perception	—users either underestimated or overestimated time	Richmon *et al.*, 1974
U.S.A.	healthy ♂	21–28	20	m,h/≥2	2–11 days	—Halstead-Reitan Battery, Time Estimation	—2 moderate and 2 heavy users performed less well on Trails B than expected on the basis of WAIS IQ scores —heavy users underestimated time intervals	Reed, 1974; Rossi and O'Brien, 1974
Denmark	♂ prisoners	17–32	64	l,m,h and other drugs/?	?	—subtests of Halstead-Reitan Battery —psychomotor function, memory	—no differences between users and controls	Bruhn and Maage, 1975
U.S.A.	students ♂, ♀	19–22	20	m,h/≥1	?	—subtests of Halstead-Reitan Battery —psychomotor performance	—no significant differences between users and controls	Hall *et al.*, 1975–76
U.S.A.	students ♂, ♀	18–22	25	m,h/2–6	"non-intoxicated"	—short-term verbal memory	—users significantly poorer than controls	Gianutsos and Litwack, 1976

TABLE 5 (CONTINUED)

Location	Description of Ss	Age (range or mean in years)	N	Extent/Duration of Use (range or mean in years)	Minimum Drug-Free Period	Test Battery	Performance of Users	Reference
U.S.A.	students ♂, ♀	24.0	10	h/2–8	1 day	—Halstead-Reitan Battery	—users outperformed controls on Trails B	Carlin and Trupin, 1977
U.S.A.	♂, ♀ (no controls)	25–36	10	h/17.4	?	—modified Michigan Neuropsychological Test Sequence	—all WAIS IQ scores in superior range; all other scores within normal range for age	Schaeffer *et al.*, 1981
Jamaica	♂	29.0	30	h/>10	4 hr	—tests of cognitive, perceptual, psychomotor function, memory, Kent IQ	—users tended to outperform controls	Bowman and Pihl, 1973
Jamaica	♂		30	h/>7	2–3 days	—subtests of Halstead-Reitan Battery —additional tests of cognitive, perceptual, psychomotor function and memory	—users significantly outperformed controls on "digit span" and were poorer on "graduated holes" tests —users outperformed controls on 29 of 47 variables	Rubin and Comitas, 1975

Greece	♂	45.9	47	h/≥10	2–24 hr	—WAIS —Raven's Progressive Matrices	—users poorer than controls on 14 of 15 variables and significantly poorer on verbal IQ, comprehension, similarities and digit symbol substitution	Kokkevi and Dornbush, 1977
Egypt	♂ prisoners	15–50	850	h/5–30	"drug-free"	—12 tests of psychomotor, perceptual, and cognitive function and memory	—users significantly poorer than controls on "H-marking," "speed," Trails A, "mark-making," "Bender-Gestalt" copy and recall, toolmatching and digits backward —users significantly better on time estimation	Soueif, 1971, 1975, 1976
Costa Rica	♂	< 50	41	h/> 10	9 hr	—Wechsler and Williams memory scales —Halstead-Reitan Battery	—no significant differences between groups —users tended to be poorer on tests of verbal and spatial memory	Satz *et al.*, 1976

TABLE 5 (CONTINUED)

Location	Description of Ss	Age (range or mean in years)	N	Extent/Duration of Use (range or mean in years)	Minimum Drug-Free Period	Test Battery	Performance of Users	Reference
India	♂ (no controls)	< 45	40	h/> 5	6 hr	—Wechsler Memory Scale —Bhatia's Battery of Intelligence —Bender Visuo-motor Gestalt	—as compared to normative scores 18% demonstrated memory impairment, 28% "mild" intellectual impairment, 20% "substantial" cognitive disturbances	Agarwal *et al.*, 1975
India	♂	18–37	23	h/> 5	12 hr	—tests of intelligence (Raven's Progressive Matrices and Malin's Test for Children) —PGI Memory Scale —other tests of perception and psychomotor function	—users significantly poorer on intelligence and memory quotients, psychomotor skills and time perception	Wig and Varma, 1977

India	♂	25–46	30	m,h/> 5	6 hr	—tests of memory (PGI Memory Scale) and psychomotor function	—no significant differences between groups other than users' poorer performance on one subset of memory scale	Ray *et al.*, 1978
India	♂	16–45	50	h/> 4	12 hr	—tests of memory, psychomotor function, perception, and cognition	—users significantly poorer on digits backward, symbol recognition, pencil tapping, reaction time, time and size estimation, and the Bender Visuo-Motor Gestalt test	Mendhiratta *et al.*, 1978

free period is stated (Table 5), it was as short as two hours (Kokkevi and Dornbush, 1977), often less than a day, and rarely longer than three days. Since cannabis intoxication can persist for several hours after administration and withdrawal symptoms for as long as a week (Jones and Benowitz, 1976), many of the investigators reporting behavioral impairment may have observed their subjects while the latter were still intoxicated or were experiencing an abstinence reaction.

Test Batteries

The psychometric tests chosen vary considerably with respect to the functions they examine, sensitivity to cognitive deficits, and degree of standardization in the observed population. Many of the test batteries employed in Jamaica, India, Egypt, Costa Rica, or Greece, that were translations or adaptations of widely used American instruments such as the Wechsler Adult Intelligence Scale (WAIS), were poorly standardized for the populations being studied. If these tests were too difficult for both users and controls, no significant differences would be apparent between the groups. Only the investigators of the Costa Rican subjects (Satz *et al.*, 1976) conducted a preliminary verification of their test battery in an attempt to rule out this "floor effect."

The most frequently used tests were some or all of the subsets of the Halstead-Reitan Battery (Table 6), an instrument sensitive to neuropsychological deficits, particularly those associated with frontal lobe function (Lezak, 1976), and that has been used successfully in discriminating groups of alcoholics from groups of nondrinking controls (Parsons and Farr, 1981; Wilkinson and Carlen, 1981). Also commonly used was the Wechsler Memory Scale which consists of seven subsets designed to assess both verbal and nonverbal memory. Descriptions and discussions of all of these tests are provided by Lezak (1976).

Results

An examination of the North American and Northern European studies (Table 5) reveals no striking differences between the performance of light, moderate, or heavy cannabis users and nonusing controls. Two groups (Entin and Goldzung, 1973; Gianutsos and Litwack, 1976) observed that controls significantly outperformed heavy users on tests of verbal memory. The results of two other groups (Richmon *et al.*, 1974; Rossi and O'Brien, 1974) suggested that there may be some disruption of time perception in heavy users.

Reed (1974) reported that two heavy users of cannabis performed less well on the Trail Making Test than would be expected on the basis of their WAIS IQ scores. However, both of these subjects had a history of LSD use. Culver and King (1974), who matched groups of users with

TABLE 6

Some Elements of The Halstead-Reitan Battery

Test	Function
WAIS	Intelligence
Category Test	Abstracting ability
Tactual Performance Test	Tactile perception and memory
Rhythm Test	Auditory perception and attention
Speech Sounds Perception Test	Auditory acuity and speech comprehension
Finger Oscillation Test	Manual dexterity
Time Sense Test	Visuo-motor reaction time and time perception
Trail Making Test (Parts A and B)	Visual conceptual and visuo-motor tracking
Aphasia Screening Test	Receptive and expressive verbal function

nonusers on the basis of predrug Scholastic-Aptitude Test scores, reported impaired performance on the same test in a group of subjects who had consumed marihuana at least twice per month and LSD at least once per month, but not in a group who smoked at least the same minimum amount of marihuana but had never used LSD. It was not reported whether the average amount of marihuana consumed differed between the two groups. Therefore, it is unclear whether higher rates of marihuana use among the LSD users, or the LSD use itself, could have contributed to this effect. On the other hand, Grant *et al.* (1973) who studied light and moderate users, found no significant differences between users and controls on the Trail Making Test. When Carlin and Trupin (1977) matched heavy users with nonusers on the basis of age, education, and Wechsler-Bellevue Full Scale IQ scores, they found that users significantly outperformed controls on the Trail Making Test (Part B). Schaeffer *et al.* (1981) reported that 10 subjects with a long history of heavy cannabis use all scored within the superior to very superior range on the WAIS IQ test, and well within the normal range for age on a variety of other tests designed to assess cognitive functioning (including the Trail Making Test). No controls were employed in this study.

The results of the so-called "foreign studies" (conducted in Jamaica, Greece, Costa Rica, Egypt, and India) varied greatly. In the two Jamaican studies (Bowman and Pihl, 1973; Rubin and Comitas, 1975), there were few significant differences between users and controls although users tended to outperform controls. The failure of Rubin and Comitas (1975) to prestandardize their test battery in a rural Jamaican population led Satz *et al.* (1976) to speculate that a floor effect may have occurred on several of the culturally biased tests. Since the raw test scores were not reported, this possibility cannot be evaluated.

The observations on chronic users in Greece (Kokkevi and Dornbush, 1977) are equally difficult to interpret. A sample of 47 heavy users, matched with 40 nonusers on the basis of age, education, origin, and upbringing, performed more poorly than the latter on 14 of 15 variables of the WAIS and Raven's Progressive Matrices Test. These differences were significant on the comprehension, similarities, and digit symbol subtests of the WAIS verbal IQ. The authors attributed the poorer performance of the users to an inadequate drug-free period before testing (in some as little as two hours) and to the better education of the controls. The latter suggestion is difficult to reconcile with the authors' previous statement that the two groups had been matched with respect to education. The former suggestion is supported by the observation of Harshman *et al.* (1976) that performance on left lateralized, verbal-analytic tasks was significantly impaired in chronically intoxicated users. On the basis of these results, Fink (1977), one of the collaborators in the Greek study, concluded that there was no evidence of cannabis-induced brain damage. Other collaborators in the same study (Stefanis *et al.*, 1976) stated that the cannabis-related "persistent effects," particularly on the digit symbol substitution test, should be further investigated.

The Costa Rican study (Satz *et al.*, 1976; Satz, 1980) was a carefully designed, thorough examination of neuropsychological functions in 41 heavy users. The test battery was pretested and modified in advance, to reduce the possibility of a floor or ceiling effect. A multivariate analysis of test results revealed no major differences between users and a control group matched for age, education, marital status, occupation, and tobacco and alcohol use. Users performed virtually identically to controls on the WAIS and the other subsets of the Halstead-Reitan Battery for which raw scores are reported. They tended to perform more poorly on tests of verbal and nonverbal memory although these differences were not significant. The impaired performance of the Greek subjects on the WAIS was not confirmed in this study, possibly because the Costa Rican users were drug-free for a longer period (at least 9 hr) before testing, while some of the Greek subjects were examined as little as 2 hr after smoking cannabis.

In a large study of Egyptian prisoners incarcerated for hashish offenses, Soueif (1971, 1975, 1976) reported in a series of papers that his group of 850 heavy users was outperformed by a control group of similar age, education, and background on a battery of 12 "objective and structured tests" of psychomotor, perceptual, and cognitive function and memory. Controls were significantly better on H-marking, Speed, Trail Making Test (Part A; Part B was not performed), Mark Making, Bender-Gestalt Copy and Recall, Tool Matching, and Digit Span Backward, while users were significantly better at time estimation. Concomitant use of opium was ruled out as a contributing factor (Soueif, 1977). The differences between users and controls were greatest in the urban, most literate, and youngest subjects. In response to speculation that this observation may have been due to a floor effect among the older, illiterate, and rural subjects (Fletcher and Satz, 1977), Soueif (1977) stated that the type of tests selected and the pattern of scatter of their scores, i.e., the lack of skewing in their distribution, make this possibility unlikely. He concluded that the degree of observed deficit may be correlated with the original level of cortical arousal which would presumably be linked to age, education, and urbanicity. In contrast, Parsons (1977) concluded that alcohol-related impairment of neuropsychological function is most apparent in alcoholics over the age of 40. This is understandable in terms of cumulative damage with longer life-time exposure. Therefore Soueif's finding of greater differences among younger subjects obviously requires a different explanation.

Soueif's observations were confirmed by an independent team of investigators in India (Wig and Varma, 1977) using a similar test battery. In addition, the subjects in this Indian study performed more poorly than a group of controls matched for age, education, and marital status on Malin's Test for Children and on the PGI Memory Scale (Indian adaptations of the Wechsler Intelligence Scale for Children and the Wechsler Memory Scale respectively).

Similar results were reported by Mendhiratta *et al.* (1978) who tested 25 Indian charas smokers, 25 bhang drinkers, and 25 nonusing controls matched for age, education, and occupation. It was found that charas smokers, estimated to have a slightly higher mean daily intake of THC than bhang drinkers, were most severely impaired. Users had significantly poorer scores on Digit Span Backwards, Symbol Recognition, Pencil Tapping, Reaction Time, Time and Size Estimation, and the Bender-Gestalt Test.

Agarwal *et al.* (1975) studied a group of 40 Indian heavy users by means of the Wechsler Memory Scale, Bhatia's Battery of Intelligence, and the Bender-Gestalt Test. As compared with normative scores for an Indian population (no controls were included), 18% of the users demonstrated memory impairment, 28% "mild" intellectual impairment, and 20% "substantial" cognitive disturbances.

On the other hand, Ray *et al.* (1978) reported no major differences on the PGI Memory Scale and other tests of psychomotor function between a group of moderate and heavy Indian cannabis users and a control group matched for age, occupation, socioeconomic status, and education. However, an examination of the raw PGI Memory Scale scores, in this and in the Wig and Varma (1977) study, reveals that both users and controls in the study by Ray *et al.* (1978) performed as poorly as the user group in the Wig and Varma (1977) study. Again, this apparent discrepancy may be an artifact of inappropriate matching of subjects or of a floor effect.

The Indian studies generally tend to confirm the observations in Egypt. However, the results must be viewed with caution since the minimum drug-free period before testing was less than 12 hr (Agarwal *et al.*, 1975; Wig and Varma, 1977; Mendhiratta *et al.*, 1978; Ray *et al.*, 1978), while Soueif's subjects were apparently drug-free for much longer periods.

Interpretation

As noted above, the interpretation of these studies is complicated by the incomplete reporting of important information by many of the authors. Descriptions of the subjects, matching procedures, extent of drug use, and test batteries were often inadequate. Data such as raw scores, standard deviations, and length of drug-free periods were also frequently omitted.

The reported test scores were almost always group means rather than individual results. With the exception of Reed (1974), who noted the unexpectedly poor performance of four users on the Trail Making Test, the authors did not report individual scores. Thus there might have been a small number of subjects in each study who would be considered clinically impaired, but who would not be revealed by an examination of the group mean scores.

In virtually all of the cross-sectional studies the selected subjects were generally healthy and seemed well-adapted in their societies. This was particularly true of the North American studies of young male university students. Only the Harvard study (Meyer *et al.*, 1974) included college drop-outs in their sample. Most samples, therefore, may have excluded individuals who for some reason (drug-induced or otherwise) could not function well enough to remain in university or even to volunteer for testing. Although Fink (1976) stated that his group was unable to find cases of cannabis-related neuropathology or psychopathology in Athens hospitals, the consistent evidence from the case reports emphasizes the fact that this possibility must be considered carefully.

It is clear from the preceding discussion that no overwhelming evidence of neuropsychological impairment has emerged from all of these studies, or even from the majority of them. This is not surprising, however, because the studies done to date were not properly designed to yield adequate epidemiological evidence, as noted above. There is an overall trend toward impairment of verbal memory and time estimation, although these findings were by no means universal. Of the tests in the Halstead-Reitan Battery, performance on the Trail Making Test was most often affected, although again, not all groups of heavy users demonstrated impairment. As Culver and King (1974) point out, there is no known type of CNS dysfunction that would impair performance on the Trail Making Tests A and B without adversely affecting the scores on other abstract tests such as the Category Test or the location score of the Tactual Performance Test. Therefore, the potential significance of the findings on the Trail Making Test is unclear.

The conflicting data from these clinical neuropsychological studies contrast with the largely consistent body of evidence in the alcohol field. Inpatient alcoholics typically perform more poorly than nonalcoholics on tests of abstracting ability, set persistence and set shifting, visuospatial problem solving, and some psychomotor functions, at a time when their verbal ability and memory are not yet demonstrably impaired (Parsons, 1977; Parsons and Farr, 1981). Even among young social drinkers, impairment of abstraction and conceptual abilities, as reflected by the Shipley Institute of Living Scale, the Halstead Category Test, and the Wisconsin Card Sorting Test, has been observed (Parker and Noble, 1977; Parker *et al.*, 1979).

Several groups have studied the neuropsychological performance of polydrug users. Koslowsky and Levett (1975), using the Shipley-Hartford Institute of Living Scale, observed an impairment in 41% of a sample of 1,980 incarcerated "narcotic addicts." McGlothlin *et al.* (1969), using the same test, observed no impairment in a group of 16 patients treated more than 20 times with LSD. Bruhn and Maage (1975) failed to demonstrate any evidence of impairment of performance on the Halstead-Reitan Neuropsychological Battery in groups of incarcerated polydrug users. Significant deficits in performance on various subtests of the Halstead-Reitan Battery were demonstrated, however, in the McGlothin *et al.* (1969) sample, as well as in groups of polydrug users (Cohen and Edwards, 1969; Grant *et al.*, 1978). Cohen and Edwards (1969) found that the degree of deficit correlated with the extent of LSD exposure, while Grant *et al.* (1978) determined that impairment was associated with the extensive use of CNS depressants and opiates, and adverse medical or developmental histories. No attempt was made in any of the studies to match users with controls on the basis of ethanol or cannabis use although the consumption of both these drugs, when reported, was heavy. It would appear, therefore, that simultaneous chronic exposure to a broad range of psychoactive substances will induce deficits in neuropsychological functioning in at least some users. It is not known, however, if any of these agents is particularly toxic, or whether drug interactions may enhance the development of organic deficits. Since street drug users tend to consume a variety of drugs, have a higher incidence of head injury (Grant *et al.*, 1978), and sometimes risk infection by using unsterilized needles and other unsanitary procedures, the separation of the various drug effects from each other and from the potential influence of other medical and environmental factors will be difficult to achieve.

Clinical Studies of Experimental Administration of Cannabis

Several groups of North American investigators have attempted to study the effects of chronic cannabis use under controlled experimental conditions. This design permits confounding factors such as nutrition, disease, and concomitant drug use to be eliminated as contributors to potential drug-induced effects. Four of these groups (listed in Table 7) have monitored brain function by means of a variety of psychometric

TABLE 7

Clinical Studies of Experimental Administration

Location	Description of Ss	Age (range or mean in years)	N	Extent of Drug Use	Amount THC Consumed (mg/day)	Duration of Administration (days)	Post-Intoxication Test Battery	Postdrug Performance	Reference
U.S.A.	healthy students ♂	22–30	5	m[a]	14	21	—short-term memory —digit symbol substitution	—improved over predrug period	Dornbush *et al.*, 1972
U.S.A.	heathy ♂	21–29	24	m,h[b]	5–10	28	—short-term memory —GDSA, computation	—no consistent differences	Frank *et al.*, 1976
U.S.A.	healthy ♂	21–35	30	m,h	35–198	64	—brain hemisphere dominance	—changes seen during chronic intoxication were not observed in postdrug tests	Harshman *et al.*, 1976
U.S.A.	healthy ♂	23.4	27	m,h	20–200	21	—simple and choice reaction time —short-term memory	—similar to or better than predrug performance	Rossi *et al.*, 1977

a. m = moderate use (1–6/week)
b. h = heavy use (⩾ once/day)

tests before, during, and after periods of chronic intoxication ranging from 21 to 64 days. The number of "joints" per day ranged from the mandatory smoking of one "joint" (Dornbush *et al.*, 1972; Frank *et al.*, 1976) to the *ad libitum* consumption of 10 or more (Harshman *et al.*, 1976; Rossi *et al.*, 1977). Short-term memory was examined by Dornbush *et al.* (1972), Frank *et al.* (1976), and Rossi *et al.* (1977); digit symbol substitution by Dornbush *et al.* (1972); goal-directed serial alternation and computation by Frank *et al.* (1976); reaction time and attention by Rossi *et al.* (1977); and brain hemisphere dominance by Harshman *et al.* (1976). The results of all of these studies are consistent in that, as compared with predrug observations, no group demonstrated any postdrug deterioration in performance. This finding is not surprising since all subjects had been moderate or heavy marihuana users for at least one year. It is unlikely, given the long-term exposure to alcohol necessary to produce behavioral impairment, that a small additional exposure of up to two months of experimental cannabis administration would suffice to produce residual deficits.

3. EXPERIMENTAL STUDIES: ANIMAL MODELS

The use of animal models, as in many areas of research, has played a valuable role in the study of cannabis-related toxicity. Despite their obvious limitations, experimental studies offer many advantages over clinical studies. By careful control of variables such as nutrition, disease, age, and environment, the effects of cannabis can be separated effectively from those of other factors. Because of the relatively short life-span of small animals, several months of drug administration can approximate several years in the life of a human, and thus long-term experimental drug administration is usually more feasible than a prospective clinical study. In addition, animals can be monitored for several months following the discontinuation of treatment, facilitating the distinction of residual drug effects from those of chronic intoxication or withdrawal. In the animal, it is also easier to correlate functional disturbances such as performance deficits with histopathology, EEG abnormalities, changes in neurochemistry, or other effects that may help elucidate the mechanism(s) of drug action.

Although acute and subchronic effects of cannabis on CNS function have been recognized for many years (Paton and Pertwee, 1973; Miller and Drew, 1974), only a small number of groups have investigated the effects of chronic intoxication. Relatively few investigators have focused on the period *following* long-term drug administration. This section provides a review of all reports describing postdrug observations following treatment during at least 14 consecutive days with cannabis extracts or with pure THC.

Brain Weight and Histopathology

Gross anatomical and histological data have been reported in a number of studies of chronic cannabis administration (see Table 8). When rats were sacrificed immediately after the end of chronic treatment, there was either no change in brain weight relative to body size, in comparison with controls (Rosenkrantz and Braude, 1974), or slight but significant increases (Rosenkrantz *et al.*, 1975; Rosenkrantz and Braude, 1976). The relative brain weights of rats allowed to recover for periods of 5 to 120 days after chronic drug administration were also no different from those of control animals (Leite and Carlini, 1974; Rosenkrantz *et al.*, 1975; Fehr *et al.*, 1979). There is no evidence that chronic administration of cannabis orally or by inhalation causes either temporary or permanent decrease in the relative brain weight of the rat.

The brains of a group of Rhesus monkeys that had been treated for 8 mo with marihuana extract (at a dose of up to 120 mg/kg Δ^9–THC per week) were examined by means of computerized tomography and angiography (Rumbaugh *et al.*, 1980). No abnormalities were apparent.

A number of investigators (also listed in Table 8) have performed histological examinations of the brains of rats and primates chronically treated with cannabis extracts or smoke, or with pure THC. When examined under the light microscope, the brains of the THC-exposed animals generally did not differ from those of controls. This was true whether sacrifice occurred immediately after drug administration (Thompson *et al.*, 1973, 1974; Rosenkrantz and Braude, 1974; Ames *et al.*, 1979; Coate and Voelker, 1979; Rumbaugh *et al.*, 1980) or after a recovery period ranging from 30 to 240 days (Stadnicki *et al.*, 1974; Rosenkrantz *et al.*, 1975; Rosenkrantz and Braude, 1976; Harper *et al.*, 1977; Fehr *et al.*, 1979). It should be noted that the reporting of data has been very inconsistent. In many cases the reader must conclude that there were no abnormalities in brain tissue only because none was mentioned in the discussion of the histopathology of organs other than the brain. Most authors have employed a hematoxylin and eosin stain, although carbol azure, luxol fast blue-cresyl violet, and phosphotungstic acid-hematoxylin stains have also yielded negative results (Ames *et al.*, 1979).

Two studies did reveal histopathological degenerative changes immediately after death or at the end of drug administration, in the brains of dogs (Durandina and Romasenko, 1972) and of rats and rabbits (Janzen *et al.*, 1978). However, the findings are difficult to evaluate since they were poorly controlled. In both studies, the doses of THC

TABLE 8

Experimental Studies of Brain Weight and Histopathology

Species	Dose/(mg/kg/day)/ Drug/Route	Duration of Treatment (days)	Recovery Period (days)	Relative Brain Weight	Type of Study	Reported Brain Histopathology	Reference
Rat	50–500/Δ^9–THC, Δ^8–THC or Δ^9–THC in CCE*/p.o.	119	none	?	l.m.[a]	—no abnormalities reported	Thompson *et al.*, 1973
Rat	0.7–4.2/Δ^9–THC in C smoke/inhalation	23	none	→[1]	l.m.	—no abnormalities reported	Rosenkrantz and Braude, 1974
Rat	20–33/Δ^9–THC in CCE/ p.o.	117	5	→			Leite and Carlini, 1974
Rat	2–50/Δ^9–THC/p.o.	180	30	→	l.m.	—no abnormalities reported	Rosenkrantz *et al.*, 1975
Rat	0.8–2.2/CBD and CBCh in C smoke/inhalation	17–25	none reported	↑[2](♂ only)			Rosenkrantz *et al.*, 1976
Rat	0.7–4.2/Δ^9–THC in C smoke/inhalation	87	20	↑at 87 days recovery data not reported		—petechial hemorrhages in animals that died during treatment	Rosenkrantz and Braude, 1976
Rat	20/Δ^9–THC, in CCE/p.o.	180	120	→	l.m.	—no abnormalities observed	Fehr *et al.*, 1979

Rat Rabbit	20/CCE/p.o.	30	none		l.m.	—hyperemia and edema —cerebral cortex, brain stem and cerebellum showed cells with degenerative changes	Janzen *et al.*, 1978
Dog	3,000/C resin/p.o.	70	none		l.m.	—degenerative changes in ganglion cells, cortex and subcortical nuclei —disappearance of Purkinje cells of cerebellum	Durandina and Romasenko, 1972
Cynomolgus monkey	~5/Δ^9–THC in C smoke/inhalation	360			l.m.	—no abnormalities reported	Coate and Voelker, 1979
Rhesus monkey	5–45/Δ^9–THC/i.v. 50–500/Δ^9–THC/p.o.	28	none	not reported	l.m.	—no abnormalities reported	Thompson *et al.*, 1974
Rhesus monkey	37.5/Δ^9–THC in CCE/p.o.	50	100		l.m.	—no abnormalities reported	Stadnicki *et al.*, 1974

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*CCE = Crude Cannabis Extract

1. → = no change
2. ↑ = increase

[a] l.m. = light microscopy
[b] e.m. = electron microscopy
[c] c.t. = computerized tomography

TABLE 8 (CONTINUED)

Species	Dose/(mg/kg/day)/ Drug/Route	Duration of Treatment (days)	Recovery Period (days)	Relative Brain Weight	Type of Study	Reported Brain Histopathology	Reference
Rhesus monkey	0.7/Δ^9–THC/i.v. or ~ 1/ Δ^9–THC in C smoke/inhalation	180	240		l.m. c.m.^{b}	—no abnormalities reported —enlarged synaptic clefts, clumping of synaptic vesicles in septal region —decreased volume density of organized rough E.R. —fragmentation and disorganization of rough E.R. with free ribosomal clusters —nuclear inclusions —changes most marked in septum, also occurred in hippocampus and amygdala	Harper *et al.*, 1977 Myers and Heath, 1979 Heath *et al.*, 1979
Rhesus monkey	~ 17/Δ^9–THC in CCE/p.o.	240	none reported		l.m. c.t.	—no abnormalities observed (4 Ss) —"equivocal" abnormalities (2 Ss) —no abnormalities observed	Rumbaugh *et al.*, 1980
Chacma baboon	20–100/Δ^9–THC, in C leaf/p.o.	240	none reported		l.m.	—no abnormalities observed	Ames *et al.*, 1979

were unspecified; in the Durandina and Romasenko (1972) experiment, they were probably very high.

The results of one study of the long-term administration of THC or cannabis smoke to the Rhesus monkey have been reported in a series of papers (Harper *et al.*, 1977; Heath *et al.*, 1979, 1980; Myers and Heath, 1979). The brains of the animals, removed 240 days after the end of 180 days of THC administration either i.v. or in cannabis smoke, were normal when examined under the light microscope. In the three treated monkeys examined, however, the electron microscope revealed what the investigators interpreted as abnormally enlarged synaptic clefts, clumping of synaptic vesicles, decreased volume density (relative volume) and fragmentation of the rough endoplasmic reticulum, and nuclear inclusions. These changes were said to be most marked in the septum, but also present in the hippocampus and amygdala. Independent investigators, however, have interpreted similar findings to be within the limits of normal variation (Moore, 1981). Because of the small number of animals involved, it is impossible to say whether the ultrastructure is indeed normal, or reflects a small but significant alteration.

On the basis of the above evidence, it would appear that chronic cannabis treatment does not result in obvious changes in brain weight, or in histopathology evident under the light microscope. The abnormalities reportedly observed under electron microscopy are suggestive of more subtle alterations in subcortical brain function, but are disputed by other neuropathologists. Clearly, additional experiments of this type are warranted.

Electroencephalography

In animal studies, electrodes may be positioned in both cortical and subcortical sites. They yield more comprehensive information than clinical EEG examinations which are virtually always limited to surface electrodes that record principally cortical activity. The experimental studies yielding postdrug information are listed in Table 9. In a few studies, rebound phenomena in the form of an increase in integrated electrocorticogram voltage, suggestive of an abstinence syndrome, appeared in the rat during the first few postdrug days and subsequently disappeared (Pirch *et al.*, 1972, 1973); in others, rebound phenomena were not observed (Moreton and Davis, 1973; Adams and Barratt, 1975). Some authors reported that certain changes observed during chronic intoxication recovered slowly over several postdrug days. These include the changes in REM sleep and time spent awake, observed in the cat by Barratt and Adams (1973), and the frequent periods of EEG

TABLE 9

Experimental Studies of EEG

Species	Dose/(mg/kg/day)/ Drug/Route	Duration of Treatment (days)	Recovery Period (days)	Electrode Placement	Postdrug Observation	Reference
Rat	20–40/Δ^9–THC in CCE*/p.o.	9–13	7	C[1]	—rebound increase of integrated ECoG voltage, maximal on postdrug days 2 and 3 —recovery by day 7	Pirch *et al.*, 1972
Rat	20–100/Δ^9–THC in CCE/p.o.	17	25	C	—rebound increase of integrated ECoG voltage, maximal on postdrug days 2–6 —recovery by days 12–17	Pirch *et al.*, 1973
Rat	10/Δ^9–THC/i.p.	19	6	C S.C.[2]	—no paradoxical sleep rebound	Moreton and Davis, 1973
Rat	20/Δ^9–THC in CCE/p.o.	180	90–180	C S.C.	—irregular spike-like waves in hippocampus persisted throughout postdrug period	Fehr *et al.*, 1976, 1979
Cat	0.17 or 2.74/Δ^9–THC or Δ^9–THC in CCE/p.o.	180	30–60	C S.C.	—slow waves and spiking in cortex subsided to a plateau 7–10 days postdrug, but remained above predrug levels	Barratt and Adams, 1972

Cat	0.34–2.74/Δ^9–THC in CCE/p.o.	180	40	C S.C.	—decrease in slow-wave sleep and increase in drowsy-light sleep persisted throughout postdrug period —drug-induced changes in REM sleep and time spent awake did recover	Barratt and Adams, 1973
Rhesus monkey	37.5/Δ^9–THC in CCE/p.o.	50	42	C S.C.	—more frequent periods of EEG desynchronization than predrug for "several" postdrug days —recovery thereafter	Stadnicki *et al.*, 1974
Squirrel monkey	1.2/Δ^9–THC/p.o.	60	30	C S.C.	—gradual increase in slow-wave sleep —no rebound phenomena —amount of time spent in Stage 1 (drowsy) remained increased	Adams and Barratt, 1975
Rhesus monkey	~1/Δ^9–THC in C smoke/ inhalation or 0.69/Δ^9–THC/i.v.	180	240	C S.C.	—spikes and sharp waves that had appeared in septum and hippocampus during treatment persisted throughout postdrug period	Heath, 1976

*CCE = Crude Cannabis Extract

1. C = Cortical
2. S.C. = Subcortical

desynchronization observed in the Rhesus monkey by Stadnicki *et al.* (1974).

In a few studies, typically those that involved the longest periods of treatment (180 days), persistent changes were observed postdrug. Irregular wave forms such as "spikes" that were evident for months after the end of treatment have been reported in the cortex of the cat (Barratt and Adams, 1972), in the hippocampus of the rat (Fehr *et al.*, 1976, 1979), and in the septum and hippocampus of the Rhesus monkey (Heath, 1976). There are no reports of persistent frequency or power changes, although the majority of investigators, including those who have observed spiking, have not employed computer-assisted analysis of the EEG recordings. Thus subtle changes in these parameters may not have been detected. Sleep studies in the cat (Barratt and Adams, 1972) and in the squirrel monkey (Adams and Barratt, 1975) suggest that the amount of time spent in drowsy sleep (Stage 1) may remain elevated for 30 to 40 days postdrug.

Thus, the reported EEG findings apparently have included cumulative but reversible drug effects, withdrawal rebound phenomena and apparently permanent drug effects. Since the implications of these are quite different, it is necessary to emphasize again the importance of differentiating clearly between them.

Neurochemistry

Changes in neurochemistry *during* cannabis intoxication have been reviewed by Rosenkrantz (this volume). Only one group of investigators has examined neurochemical changes in the period *following* chronic intoxication. Luthra *et al.* (1975b) reported no change in protein and RNA levels, but an increased acetylcholinesterase activity in the cerebrum and cerebellum of both male and female rats 30 days after 180 consecutive days of oral treatment with up to 50 mg/kg THC daily. Similar findings were reported in rats 20 days after 87 days of administration of marihuana smoke delivering up to 4 mg/kg THC, except that the changes in acetylcholinesterase activity were less consistent (Luthra *et al.*, 1976). Throughout both experiments the alterations in acetylcholinesterase levels coincided with behavioral changes associated with cumulative toxicity. These rats also demonstrated sporadic changes in glycolytic enzymes (Luthra *et al.*, 1975a), which do not lend themselves to any coherent and comprehensive interpretation.

Much more work is obviously required to clarify the significance of the neurochemical observations. An integrated approach correlating behavioral or physiological changes with the endogenous levels and turnover rates of as many substances as possible in discrete areas of the brain would be helpful in this respect.

Behavioral Toxicity

Postnatal Exposure

The technique of experimental observation of behavior has been found, by a number of investigators, to be one of the most sensitive measures of CNS dysfunction caused by various drugs and environmental agents (Weiss and Simon, 1975). Only relatively recently have studies of cannabis toxicity included significant periods of postdrug data collection.

In most of these studies (listed in Table 10), the postdrug period has been short and the observations have been mainly of spontaneous behavior or of performance on an operant task learned before the initiation of drug administration. The increased grooming scores of rats during the open-field test 4 days after 19 days of treatment (Sjöden *et al.*, 1973) and the increased aggression in dominant mice seven days after 14 days of exposure (Cutler *et al.*, 1975) probably represent continuation of drug effects rather than residual postdrug effects. The postdrug recovery period was too short to permit complete clearance of the cannabinoids, and the administration periods were probably too short to have caused lasting effects.

Virtually all of the investigators observing disruptions of gross behavior or maintained disturbances of operant behavior during drug administration reported a return to baseline behavior within 15 postdrug days (Ferraro and Grilly, 1973, 1974; Frankenheim, 1974; Stadnicki *et al.*, 1974; Giono-Barber *et al.*, 1974, 1975; Luthra *et al.*, 1975b, 1976; Rosenkrantz *et al.*, 1975; Manning, 1976; Levett *et al.*, 1977). Snyder *et al.* (1975) did observe unstable response rates on a tandem differential reinforcement of low rate/fixed-interval (DRL-FI) schedule in the stump-tailed macaque 14 days after 90 days of oral administration of THC. However, the animals were treated only on every third day with a dose (2 mg/kg) that did not produce any apparent intoxication on the day following each administration. The absence of sustained intoxication, therefore, makes the significance of this finding unclear. In two studies, Barratt and Adams (1972, 1973) noted that the drug-induced lethargy, lack of playfulness, and body swaying persisted in the cat for up to 60 days postdrug. This was associated with a persistent increase in the time spent in drowsy (Stage 1) sleep (Barratt and Adams, 1973) and persistent slow waves and spiking in the cortical EEG recordings (Barratt and Adams, 1972).

Only two groups have examined the acquisition of new behavior

TABLE 10

Experimental Studies of Residual Effects on Behavior

Species	Dose(mg/kg/day)/ Drug/Route	Duration of Treatment (days)	Observations During Treatment	Duration of Recovery Period (days)	Observations During Recovery Period	Reference
Mouse	$\sim 30/\Delta^9$–THC in CCE*/p.o.	14	—reduction of nonsocial activity —increase in flight, social and sexual interaction in dominant mice	7	—increased aggression in dominant animals	Cutler *et al.*, 1975
Mouse	$10/\Delta^9$–THC/i.p.	20–40	stimulation followed by depression progressed to hyperexcitability and aggression	200	—gradual decrease in hyperexcitability —impaired retention of avoidance behavior at postdrug days 2 and 100	Radouco-Thomas *et al.*, 1976
Rat	$2.5/\Delta^9$–THC/i.p. or $5/\Delta^8$–THC/i.p.	19	—decrease of ambulation, rearing, grooming, latency to leave start on open-field test	4	—most measures returned to normal —grooming scores showed a rebound increase	Sjöden *et al.*, 1973
Rat	up to $32/\Delta^8$–THC/i.p.	30	—disruption of DRL performance	9	—complete recovery by postdrug day 1	Frankenheim, 1974

Rat	30/Δ^9–THC/p.o.	10–45	—disruption of Sidman avoidance performance	10–20	—shock rates in non-tolerant rats slowly returned to baseline over postdrug days 5–15	Manning, 1976
Rat	20/Δ^9–THC in CCE/ p.o.	180		30–60	—impaired Hebb-Williams maze performance —impaired learning of treadmill pacing —muricide	Fehr *et al.*, 1976, 1979
Rat	20/Δ^9–THC in CCE/ p.o.	40–180		$\geqslant 30$	—90 or 180 days of treatment produced: —impaired learning of treadmill pacing —impaired acquisition of radial maze and DRL tasks —lack of habituation on open field —faster learning on 2-way shuttle-box avoidance	Stiglick and Kalant, 1982a and b
Rat	8.8/Δ^9–THC in CCE/i.p.	45	—muricide in food-deprived rats	5	—muricide persisted even though food was restored	Alves and Carlini, 1973

*CCE = Crude Cannabis Extract

TABLE 10 (CONTINUED)

Species	Dose(mg/kg/day)/ Drug/Route	Duration of Treatment (days)	Observations During Treatment	Duration of Recovery Period (days)	Observations During Recovery Period	Reference
Rat	2–50/Δ^9–THC/i.p.	35–60	—muricide —compulsive motor routines	7	—muricide continued in all killers	Miczek, 1976, 1979
Rat	6.0/Δ^9–THC/i.p.	30	—muricide dependent on feeding and housing	20	—muricide persisted in isolated rats, disappeared in grouped rats	Ueki *et al.*, 1972
Rat	2–50/Δ^9–THC/p.o.	180	—initial depression followed by irritability, hyperactivity, aggression, tremor and clonic convulsions	30	—no abnormal behavior	Luthra *et al.*, 1975 Rosenkrantz *et al.*, 1975
Rat	0.7–4.2/Δ^9–THC in C smoke/inhalation	87	—CNS depression followed by stimulation (irritability, hyperactivity, aggression, etc.)	20	—"generally" normal behavior	Luthra *et al.*, 1976
Rat	20–33/Δ^9–THC in CCE/p.o.	126	—no change in home cage or on open field	5	—normal behavior	Leite and Carlini, 1974

Cat	0.17 or 2.74/Δ^9–THC or Δ^9–THC in CCE/p.o.	180	—fixation behavior, ataxia, tremor, body swaying, lethargy	30–60	—lethargy recovered by postdrug day 7 —body swaying persisted throughout postdrug period	Barratt and Adams, 1972
Cat	0.34 or 2.74/Δ^9–THC in CCE/p.o.	180	—lethargy, less playful	40	—lethargy and lack of playfulness persisted throughout postdrug period	Barratt and Adams, 1973
Chimpanzee	1.0 or 4.0/Δ^9–THC/p.o.	21–42	—impairment of accuracy and speed on matching-to-sample	21–33	—baseline performance recovered within 7–12 days postdrug	Ferraro and Grilly, 1973
Chimpanzee	1.0/Δ^9–THC/p.o.	152	—impairment of accuracy on matching-to-sample task	42	—baseline performance recovered within 10 days postdrug —no residual effects on 3 different probe tests at 20, 31, and 42 days postdrug	Ferraro and Grilly, 1974
Rhesus monkey	37.5/Δ^9–THC in CCE/p.o.	50	—sedation followed by tolerance	>100	—increased aggression 2–7 days postdrug —no abnormal behavior seen after 7 days postdrug	Stadnicki *et al.*, 1974
Stump-tailed macaque	2.0/Δ^9–THC/p.o.	every 3rd day for 90	—disruption of performance on tandem DRL-FI schedule on drug days	14	—unstable rates of response during post-drug period	Snyder *et al.*, 1975

TABLE 10 (CONTINUED)

Species	Dose/(mg/kg/day)/ Drug/Route	Duration of Treatment (days)	Observations During Treatment	Duration of Recovery Period (days)	Observations During Recovery Period	Reference
Cynocephalus monkey	1.8/Δ^9–THC in C resin/p.o.	35	—depression followed by hyperactivity and aggression	14	—behavior slowly returned to normal	Giono-Barber *et al.*, 1974
Cynocephalus monkey	1.8 or 2.6/Δ^9–THC in C resin/p.o.	20	—CNS depression —impaired acquisition and performance of a color selection task	15	—performance returned to baseline within 5–10 days postdrug	Giono-Barber *et al.*, 1975
Chacma baboon	100/Δ^9–THC in C leaf/p.o.	14	—increased social activity —vocalization —decreased aggression	10	—no abnormal behavior reported	Levett *et al.*, 1977

following a long period of chronic intoxication. Radouco-Thomas *et al.* (1976) reported an impairment of the acquisition and retention of avoidance behavior, relative to untreated controls, in three strains of mice 2 and 100 days after 20 to 40 days of i.p. administration of THC. By postdrug day 200, the differences between drug-exposed and control mice were no longer evident, presumably because of an age-related deterioration in the performance of all groups. Fehr *et al.* (1976, 1979) observed impaired Hebb-Williams maze performance and impaired learning of a treadmill pacing skill in rats 30 to 60 days after 180 consecutive days of oral treatment with cannabis extract. These findings were later confirmed and extended by Stiglick and Kalant (1982a and b) who, in addition to the slower learning of the treadmill pacing, also observed after 90 or 180 days of chronic administration and 30 to 90 drug-free days, a much more marked impairment of acquisition of performance on the radial maze and of acquisition of a food-reinforced complex operant behavior (DRL), which requires accurate time estimation as well as other cognitive skills. In addition, the exposed rats demonstrated a lack of habituation on the open-field test and faster learning of a two-way avoidance task. The latter two observations are suggestive of impaired inhibitory control of behavior, and are seen in animals with hippocampal lesions. For the first time, an approximate exposure threshold was established: 40 days of treatment failed to elicit lasting behavioral impairment, but 90 days at the same dose did so. On the other hand, Ferraro and Grilly (1974), who exposed chimpanzees to Δ^9-THC orally for 152 days, increased the complexity of their matching-to-sample task on postdrug days 20, 31, and 42. They found no drug-related residual effects on the three probe tests.

A number of investigators have observed a typical muricidal behavior in rats during the drug-free period following chronic cannabis or THC administration (Ueki *et al.*, 1972; Alves and Carlini, 1973; Miczek, 1976, 1979). This behavior was initiated during chronic intoxication and persisted for up to 20 days thereafter. Fehr *et al.* (1979), however, noted muricide in 70% of rats exposed to mice for the first time 30 to 60 days postdrug, while 90% of the controls were nonkillers. This suggests that the tendency to muricide does not require exposure to mice during or immediately after drug treatment. The appearance of muricide is highly strain-dependent (Miczek, 1979) and is also more prevalent under conditions of food deprivation (Ueki *et al.*, 1972; Alves and Carlini, 1973) and isolation (Ueki *et al.*, 1972). In a recent experiment, Fujiwara and Ueki (1979) found that muricide, infanticide, and other signs of increased aggression persisted for up to 100 days in isolated rats administered an acute i.p. injection of 6.0 mg/kg THC. These behaviors temporarily disappeared when the rats were housed in groups. Thus even limited exposure to cannabis may interact with other stress-related factors to produce specific types of aggressive behavior that continue for as long as the conditions of stress are maintained. The significance of this abnormal predatory behavior, in terms of behavioral toxicity, is unknown.

In summary, in most studies there appears to be little or no residual drug effect on gross or previously established operant behaviors. Chronically treated animals, however, appear to be at a disadvantage when learning new skills, a task that is considerably more complex than repeating previously acquired skills. Thus it would appear that cannabis-induced residual deficits are evident only when the behavioral demands on the animal are high. It would follow that these deficits are rather subtle. It is interesting to note that rats exposed for 180 days to a daily dose of ethanol (6 g/kg), sufficient to produce a degree of intoxication roughly similar to that observed in the cannabis-exposed animals, demonstrated a degree of residual behavioral impairment comparable to that of the latter group (Fehr *et al.*, 1976, 1979). Other types of ethanol-related behavioral deficits have also been observed several weeks postdrug in the mouse (Freund and Walker, 1971) and in the rat (Walker and Freund, 1971, 1973; Bond and DiGiusto, 1976).

Relevance of Postnatal Studies

As noted above, residual changes following chronic postnatal exposure to cannabis have been reported in brain ultrastructure (Harper *et al.*, 1977; Heath *et al.*, 1979; Myers and Heath, 1979), in EEG recordings (Barratt and Adams, 1972; Heath, 1976; Fehr *et al.*, 1976, 1979), in sleep patterns (Barratt and Adams, 1972), in neurochemistry (Luthra *et al.*, 1975a and b, 1976), in spontaneous behavior (Barratt and Adams, 1972, 1973), and in complex behavior (Radouco-Thomas *et al.*, 1976; Fehr *et al.*, 1976, 1979; Stiglick and Kalant, 1982a and b). If the oral and inhaled doses administered in all these studies are recalculated in relation to body surface area, they are well within the range specified by Rosenkrantz (this volume) for each species as being comparable to heavy use (up to 6 “joints” per day) in the human. In the rat, administration of 2 to 4 mg/kg THC in cannabis smoke (equivalent to 6 to 12 mg/kg administered orally) produces plasma THC concentrations of 25 to 300 ng/ml, a range similar to that of peak concentrations observed in man after inhaled doses of 0.05 to 0.16 mg/kg (Rosenkrantz and Fleischman, 1979). Clearly, future studies of CNS function in different species will have to include estimation of peak plasma THC levels so that the equivalence of the experimental doses can be specified more exactly.

Although attempts have been made to correlate the behavioral observations with other manifestations of CNS dysfunction (Barratt and Adams, 1972, 1973; Luthra *et al.*, 1975b, 1976; Fehr *et al.*, 1979), the findings have not been particularly enlightening. Future investigation in this area should benefit from the earlier demonstrations of the dose levels and lengths of exposure necessary to produce residual change.

Prenatal Exposure

It has been recognized for many years that behavioral toxicity could appear in the absence of gross disturbances of morphology in the offspring of mothers treated during pregnancy with low doses of a number of psychoactive drugs and environmental agents. A number of reviews of this field of "behavioral teratology" have appeared (Coyle *et al.*, 1976; Hutchings, 1978; Rodier, 1978). Again, it appears that late postnatal behavioral aberrations are one of the most sensitive indicators of CNS malfunction induced by prenatal drug exposure.

The studies in which possible behavioral teratogenicity of cannabis has been sought are listed in Table 11. An examination of the table reveals major differences both in experimental design and in results. Variations in dose, routes of administration, fostering techniques (important for the separation of prenatal from postnatal effects), age at testing, and behaviors studied probably explain the apparently conflicting observations. In addition, only two groups of investigators (Abel, 1979; Charlebois and Fried, 1980) controlled for maternal nutrition. This factor is important because the initial anorexic effects of cannabis in the rat may contribute to malnutrition of the mother during pregnancy (Abel, 1980). An analysis of the body composition of neonates exposed *in utero* to cannabis extract revealed a pattern of changes similar to that observed after malnutrition studies (Greizerstein and Abel, 1981). In addition, Charlebois and Fried (1980) reported that cannabis-induced impairment of development was exacerbated in the pups of rats fed a low-protein diet during pregnancy, and was ameliorated in the offspring of those fed a protein-enriched diet.

Another problem is that most authors have selected at random a small group of offspring from an even smaller number of litters. Because of genetic similarities, the within-litter variance may be less than the between-litter variance, and therefore the litter, rather than the individual offspring, may be a more appropriate unit of statistical analysis (Abbey and Howard, 1973). To overcome these problems, an increase in the number of litters and estimates of within- and between-litter variance would be necessary.

Potential sex-related differences in drug sensitivity have also largely been ignored. Although Fried (1976) and Fehr *et al.* (1979) reported no difference between males and females, Abel (1979) observed

TABLE 11

Experimental Studies of Behavioral Teratology

Species	Dose/(mg/kg/day)/ Drug/Route	Fetal Toxicity	Fostering	Age at Testing (days)	Behavior	Reference
Rat	250/CCE*/s.c.	none	none	65	—no abnormal development —impaired learning in Lashley III maze	Gianutsos and Abbatiello, 1972
Rat	10/Δ^9–THC/s.c.	none	X-foster		—growth retardation —delayed incisor eruption	Borgen *et al.*, 1973
				9	—delayed cliff avoidance and visual placing reflexes	
				13 and 17	—hyperactivity in open field, decrements in grooming and rearing	
Rat	30–120/Δ^9–THC/s.c.	increase in perinatal mortality and morbidity	split-litter foster and X-foster	16	—decrease in spontaneous activity	Uyeno, 1973
				20	—2 channel maze—normal behavior	
Rat	2/Δ^9–THC/p.o.	none	none	20	—no change in open field —increased aggression in push tube —impaired acquisition of passive avoidance behavior	Vardaris *et al.*, 1976
				90	—increased aggression in push tube —passive avoidance normal	

Rat	∼13/Δ^9–THC in C smoke/inhalation	decreased birthweight	split-litter X-foster	 9 14	—delayed incisor eruption —delayed eye opening —decrease in spontaneous activity —normal spontaneous activity	Fried, 1976
Rat	∼16/Δ^9–THC in C smoke/inhalation	decreased birthweight	none	9 and 14	—delayed incisor eruption —delayed eye opening —delayed visual placing reflex —decrease in spontaneous motor activity	Fried and Charlebois, 1979b Charlebois and Fried, 1980
Rat	10/Δ^9–THC in CCE/p.o.	none	whole-litter foster X-foster	65	—no difference in Hebb-Williams maze performance	Fehr *et al.*, 1979
Rat	50/Δ^9–THC in CCE/p.o.	not reported	surrogate fostering	75	—no effect on spontaneous alternation, discrimination, shock avoidance or open-field behavior —♀-impaired roto-rod (motor) performance	Abel, 1979
Rat	1-10/Δ^9–THC/p.o.	embryocidal effects at higher doses	none	∼30	—offspring hypersensitive to a test dose of 10 mg/kg THC p.o. —10%–25% responded with involuntary vertical jumping	Rosenkrantz, 1979

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*CCE = Crude Cannabis Extract

TABLE 11 (CONTINUED)

Species	Dose/(mg/kg/day)/ Drug/Route	Fetal Toxicity	Fostering	Age at Testing (days)	Behavior	Reference
Rat	4.3/Δ^9–THC in C resin/i.p.	none	none	18	—increased exploration in open-field test	Kawash *et al.*, 1980
				21	—impaired performance in water maze	
Rhesus monkey	2.4/Δ^9–THC/p.o.	one offspring died at birth with neuro-histopathology	none	?	—one offspring—normal social interaction but hyperactive	Sassenrath and Chapman, 1975
Rhesus monkey	2.4/Δ^9–THC/p.o.	not reported	none	?	—alteration in regulation of visual attention	Golub *et al.*, 1979

that female offspring tended to perform more poorly than males on the roto-rod test. This factor deserves careful examination.

In summary, the results of these experiments have been inconsistent. Where present, deficits have appeared in the form of delayed development such as late eye opening (Fried, 1976; Fried and Charlebois, 1979b) and incisor eruption (Borgen *et al.*, 1973; Fried, 1976; Fried and Charlebois, 1979b) and delayed cliff avoidance and visual placing reflexes (Borgen *et al.*, 1973; Fried and Charlebois, 1979b). Delayed incisor eruption was also reported in the offspring of rats treated with cannabis smoke prior to conception (Fried and Charlebois, 1979b). It is of interest that developmental abnormalities similar to those reported by Fried (1976) were also found in the second generation of the same offspring (Fried and Charlebois, 1979a). Disruption of open-field behavior occurred only on testing before 20 days of age (Borgen *et al.*, 1973; Uyeno, 1973; Fried, 1976; Fried and Charlebois, 1979b; Kawash *et al.*, 1980). Studies of offspring tested at a later age revealed fewer abnormalities, although increased aggression was reported by one author (Vardaris *et al.*, 1976). The effects of prenatal exposure to ethanol are also more evident in younger offspring (Bond and DiGiusto, 1977). Because of the plasticity of the infant brain, it may be that prenatally induced deficits are reversible during the first few weeks of life.

Rosenkrantz (1979) reported that 30-day-old rat pups exposed *in utero* to THC were hypersensitive to a test dose of 10 mg/kg, and approximately 10%–20% responded with involuntary vertical jumping ("popcorn" response). This reaction also appears as a sign of neurotoxicity in chronically treated adult rats (Luthra *et al.*, 1976).

The appearance of cannabis-induced deficits did not seem to depend on whether the drug was administered for a limited duration or throughout pregnancy, although Fried and Charlebois (1979b) observed that drug effects were attenuated in the offspring of rats chronically exposed prior to and throughout gestation. Possibly the development of tolerance to the anorexiant effects of cannabis before pregnancy resulted in normal maternal nutrition during pregnancy, and thus removed one indirect mechanism of fetal damage.

It is noteworthy that at 65 days of age, the offspring of cannabis-treated rats were not impaired on the Hebb-Williams maze (Fehr *et al.*, 1979), a test that is sensitive to residual deficits induced by both cannabis (Fehr *et al.*, 1976) and ethanol (Bond and DiGiusto, 1976) in adult rats. Thus the signs of cannabis-induced behavioral teratology appear to be at least as subtle as, or even more subtle than, those of residual toxicity. It would be interesting to know whether a complex task such as the DRL schedule, which seems to be the test most sensitive to cannabis-induced deficits in adult rats (Stiglick and Kalant, 1982b) might also be affected by prenatal cannabis treatment.

4. CONCLUSIONS AND RECOMMENDATIONS

On reviewing the literature on cannabis and CNS function, one is immediately struck by major differences in data generated by various types of studies. Patients who have presented themselves for treatment of assorted psychiatric and neurological symptoms have demonstrated behavioral abnormalities characterized by lethargy and difficulties with perception, memory, and concentration. These symptoms appear to be associated with prolonged heavy cannabis intoxication and are particularly obvious when THC consumption exceeds 1,000 mg/day (Tennant, 1981). They disappear, for the most part, when the use of cannabis is discontinued. Some users, however, may continue to exhibit symptoms for many months postdrug. These observations are supported by evidence from animal models, which suggests that although many behaviors return to normal following termination of chronic drug administration, the performance of complex tasks may remain impaired. Residual subcortical EEG abnormalities accompanied by septal and hippocampal ultrastructural changes have also been claimed (Heath *et al.*, 1979).

On the other hand, cross-sectional studies of healthy nonintoxicated heavy users in the U.S.A., Jamaica, and Costa Rica have largely failed to produce convincing evidence of neuropsychological impairment. The poor performance relative to controls demonstrated by Greek and Indian subjects may have resulted from the fact that the users were tested while still intoxicated. In cross-sectional studies, only the presumably drug-free Egyptian subjects have provided strong evidence of a long-term cannabis-induced behavioral impairment.

There are probably several reasons for the apparent disagreements. The most obvious is variation in sample selection. It is not surprising that cannabis-related symptoms are most prevalent in subjects who have presented themselves for medical treatment, and that they are not reported frequently in populations selected on the basis of good health. The lack of positive findings in the cross-sectional studies involving small numbers of subjects suggests that these symptoms occur in a relatively small percentage of cannabis users. Affected individuals, therefore, may not have been represented in a sample of only 10 to 50 users. In a study of 1,001 inpatient alcoholics who had consumed at least 80 g ethanol per day for a mean of 20 yr, Ashley *et al.* (1981) reported that cirrhosis was found in only 6.5% and clinically evident organic brain disease in 5.1%. These disorders, generally accepted to be associated with alcoholism, would probably have been missed in a sample consisting of 50 daily drinkers of ethanol, some of whom might have consumed only 10 to 20 g daily.

In contrast, Soueif (1971, 1975, 1976) studied 850 Egyptian users and controls. With a sample of this size, he was more likely to find that differences between users and nonusers were statistically significant. It was also more probable that he would find cannabis-impaired individuals in such a large group. Wide-scale epidemiological studies will be necessary to resolve this issue.

Cross-sectional studies also suffer from the problem of *post hoc* matching of users with nonusing controls. With the exception of Culver and King (1974) who matched their subjects on the basis of predrug scholastic aptitude scores, all investigators have matched users after many years of drug consumption with nonusers of similar age, education, socioeconomic status, etc. If chronic drug use had impaired performance and thus lowered the socioeconomic status of the users, this type of matching could minimize the differences between users and nonusers. Alcohol consumption is an additional factor that must be considered when one matches users with controls, since even "social drinking" is reported to affect psychoneurological test scores (Parker and Noble, 1977).

Contributing to the problem of sample selection in the cross-sectional studies is the fact that the reported data consist of, at best, only the group mean scores. If behavioral impairment is relatively rare, a small number of users may demonstrate poor performance, but this might not markedly affect the mean score. Reed (1974) did find that 2 of 10 heavy users performed poorly on the Trail Making Test. In fact, one or two poor performances might increase the within-group variance to the point that between-group differences may not be statistically significant. For this reason, the systematic reporting of aberrant scores in small samples of users is necessary.

There is also very little overlap in the types of data yielded by the various types of studies. For example, none of the behavioral observations described clinically was complemented by neuropsychological testing. It is unclear whether clinically impaired patients would demonstrate objective evidence of brain damage. A predrug psychiatric examination of 2 of the 10 heavy users initially selected for the Harvard study of experimental administration revealed deficits in abstracting ability and apparent lapses in attention (Meyer *et al.*, 1974). It was not stated, however, whether these were the same two heavy users who performed poorly on the Trail Making Test (Reed, 1974). Kuehnle *et al.* (1977), who reported normal computerized axial tomographic scans in 19 heavy users as part of the same study, did not state whether the behaviorally impaired subjects were included in this sample.

It is very evident from the body of the review and from the above discussion that important data have frequently been omitted from the clinical and experimental reports. There is a clear need for accurate reporting of such information as extent of drug exposure, peak plasma levels of THC, length of drug-free periods before testing, and individual scores, as well as group test scores and standard deviations, and this should be accompanied by observations of gross behavior and other quantitative studies of CNS function and morphology.

Despite the above limitations, most of the evidence points to the fact that cannabis-related changes occur only with heavy prolonged use. They are also rather subtle, and are not usually evident if only simple behaviors are examined. The behavioral abnormalities do not appear to be manifestations of gross brain alteration. Probably the most serious disturbances described in the clinical literature are manifestations of chronic intoxication. At present, evidence supporting the existence of a residual alcohol-induced cerebral pathology in man (Parsons and Farr, 1981; Wilkinson and Carlen, 1981) is much more convincing than the evidence for corresponding residual damage after cannabis use. This may simply be a result of more and better controlled research in the alcohol field.

On the basis of the above review, several recommendations for future research can be made. The proposed studies should be helpful in resolving the conflicts that appear in the present literature.

The experimental design in future work must be considered carefully. Greater selectivity in the recruitment of subjects and the choice of test procedures is necessary to answer specific questions raised by the clinical observations. There is also a need for long-term follow-up observations during specified cannabis-free periods, so that the degree of reversibility of chronic drug effects can be established. More attempts should be made to correlate clinical observations with the results of objective neuropsychological tests and with other measures of CNS function.

Wide-scale epidemiological observations with well-defined questions are essential to ascertain the prevalence of the clinically reported behavioral impairments in various populations and to fulfill the statistical requirements necessary for the establishment of a cause-and-effect relationship (Mausner and Bahn, 1974). A low prevalence would explain the generally negative findings of the small-sample cross-sectional studies. Comparative studies with other drugs will help investigators to evaluate the neurotoxicity of cannabis in a broader context.

Longitudinal studies including behavioral observations before, during, and after years of chronic drug use would of course be ideal. It is hoped that the future clinical evidence will suggest questions sufficiently precise to justify the huge expense of such an undertaking.

Experimental studies will also be helpful in the correlation of behavioral effects with other changes in CNS function and structure, and in the elucidation of mechanisms of drug action. For example, a confirmation of, or failure to confirm, the ultrastructural changes reported by Heath (1979) would be extremely valuable, especially if accompanied by observations of subtle and complex behaviors.

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Psychiatric Effects of Cannabis Use

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1. INTRODUCTION

Cannabis is used mainly because of its mood-altering and psychoactive properties; consequently, the probability that this practice might entail psychological damage to those indulging in it has been a matter of much concern among health professionals. This concern is reflected in the amount of effort and material resources invested over years in search of answers to a basic question: Is cannabis capable of causing psychiatric illness?

This specific aspect of cannabis research, however, appears to have received considerably more attention during the 1960s and early 1970s than in recent years, particularly in North American and other industrialized societies where the habit became significantly prevalent during that period.

Several factors may have contributed to the recent decline in interest in the study of the psychiatric implications of cannabis use: the apparent scarcity of cases seeking treatment in clinical facilities is one of them. While the numbers of people using cannabis have grown steadily year by year, the demand for psychiatric services has remained consistently low. Cannabis cases, or at least those identified as such, do not amount to any significant proportion of psychiatric patients. With the possible exception of countries in North and West Africa and in the Indian subcontinent, where the diagnosis of cannabis psychosis is more readily made, and in Latin America, where psychiatric services are forced to accept referrals from legal agencies, mental health professionals around the world have not been hard pressed to assign a high priority to this problem in recent years.

Scientific interest in cannabis-induced psychopathology as deter-

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mined by clinical studies and in laboratory experiments with human subjects may also have lessened as a consequence of the limited results obtained thus far. Research work in this area appears to have reached a dead end and, for some time now, funding agencies have tended to switch their support towards other areas of cannabis investigation which seem more promising. A recent monograph, *Marijuana Research Findings*, issued by the U.S. Department of Health and Human Services (Petersen, 1980) as well as its Annual Reports on Marihuana and Health for the period 1977 to the present (U.S. Secretary of Health, Education and Welfare, 1979a, 1980) stress the "little new evidence" available on the subject of cannabis and psychopathology, and tend to restate observations collected mainly before 1976.

Scientific work on this matter may also have been influenced by prevailing social attitudes: although still illegal, the use of cannabis by large sectors of the population, particularly adolescents and young adults, is being more and more tolerated. Health professionals, along with society at large, seem to have stopped worrying about its psychiatric consequences. Complacency, increasingly, is replacing the somewhat exaggerated alarm that was exhibited by scientists and clinicians a few years ago. Both of these attitudes are detrimental to the progress of knowledge—exaggerated alarm because it discredits scientific research, and complacency because it leads to neglect and the surrendering of professional responsibilities.

The accumulated evidence on the association between cannabis use and psychiatric disturbance has been thoroughly reviewed in several writings during the last 10 yr (for example, WHO Scientific Group, 1971; Le Dain, 1972; Negrete, 1973; Halikas, 1974; Meyer, 1975; Edwards, 1976; Granville-Grossman, 1979; U.S. Secretary of Health, Education and Welfare, 1979a, 1980). The present paper constitutes an attempt to identify those findings which are supported by the largest consensus, as well as the issues which, in the author's judgment, remain unresolved.

2. PSYCHIATRIC IMPLICATIONS OF EPIDEMIOLOGICAL TRENDS

In most populations that have been periodically surveyed, the extent of cannabis use has shown an increase over the years. The practice is becoming more and more widespread, particularly in certain industrialized Western countries. In North America, for instance, cannabis use has already been adopted by a majority of individuals within certain specific age groups. Not only is cannabis being used by greater numbers, there is also a tendency towards a younger age of onset of use. In addition, varying patterns of use are being more clearly differentiated and it would now appear pertinent to separate the average user from the "deviant" one with respect to the psychopathological implications of their behavior (Jessor, 1979).

Epidemiological trends have important psychiatric implications. The larger the sector of population involved in cannabis use, the less relevant becomes the role of individual psychopathology among the factors determining the adoption of this habit by a given person. The degree of psychiatric problems associated with the habit depends largely on the type of population practising it. Psychiatric disturbance is likely to be more pronounced in users who constitute a deviant group, i.e., those socially and psychologically alienated from the majority.

The emphasis of psychiatric reports appearing in the literature over the years tends to confirm these assertions. Lambo (1965), for instance, discussing the problem of drug abuse in West Africa some 20 yr ago, tended to equate the mere use of cannabis with psychopathology, perceiving it as being one of a host of manifestations of psychological disturbances. Others were crime, alcoholism, delinquency, gangsterism, and prostitution. Sharma (1975) describes cannabis users in Nepal as "low calibre" persons who cannot be relied upon. In a Colombian rural area, a member of the upper social strata who uses marihuana is labeled *marijuanero*, a term which implies not only that the person uses cannabis, but also that the person is morally and psychologically deranged. Such an attitude is not held among the lower classes where the habit is more widespread (Partridge, 1975). Hutchinson (1975) asserts that, during the 1950s, marihuana users in Brazil were to be found among the "poor, prostitutes, unemployed and troublemakers."

At the present time, the habit has expanded well beyond the limit of such selective groups almost everywhere in the world, but particularly so in the industrialized countries of the West. In North America, this expansion appears to be occurring at a quicker pace than elsewhere. Cannabis prevalence data, collected at similar points in time among comparable populations, reveal a much higher percentage of users in Canada than in Mexico, Colombia, or Brazil (Negrete, 1976). Given the differences in user selectivity that these figures imply, it could be expected that the degree of personality deviance or psychopathology associated with the habit would not be the same in different societies.

In a recent review of psychosocial research on marihuana, Jessor (1979) asserts that as its use becomes more embedded in the prevailing culture, the study of personality characteristics of users becomes less relevant. He suggests strongly that concern should shift from the question of mere use to that of abuse. He quotes field researchers whose findings indicate that, unlike the situation that existed until recently, the contribution of demographic and environmental attributes to the variance in rates of marihuana use is becoming increasingly less important in the U.S. In that country, the most important factors that determine whether or not an individual starts smoking marihuana are: having a friend who does it, and being at a place where the drug is available. Since both these conditions are common in societies where the habit has become widespread, individual psychopathology can no longer be considered a *sine qua non* factor in the initiation of this behavior. In addition, recent field studies comparing the degree of psychopathology in users and nonusers have failed to elicit significant differences between them (Jessor, 1979).

During the 1960s and early 1970s, cannabis users were generally perceived, and tended to perceive themselves, as a rather homogeneous group among whom the various patterns of use made no difference. It would appear now that norms are being established as to when, where, how often, and in what quantities it is admissible to use the drug. A notion of "deviance" is developing among users and they are starting to view heavy consumers as "problem" cases.

A national survey of high school seniors in the U.S. has found that while 6 of 10 respondents admitted to using cannabis, daily use is limited to approximately 10% of the population studied (Johnston *et al.*, 1977). Comparative studies focusing on personality variables found a significant positive correlation between degree of psychopathology and heavy use (Mirin *et al.*, 1971; Cross and Davis, 1972; Wells and Stacey, 1976; Mendhiratta *et al.*, 1978). Weller and Halikas (1980) have found that "problem users" are six times more likely to indulge in heavy use than regular marihuana smokers who deny having experienced difficulties related to the habit. Thus, heavy use is still atypical in Western societies, and is associated with a higher risk of psychopathology.

A review of the U.S. National Statistics for 1979 indicates that, in contrast to the limited percentage of daily users found by Johnston *et al.* (1979) among high school seniors (10.3%), such heavy users represent 43% of the new cases registered that year in the network of government-supported drug treatment centers across the nation (U.S. Secretary of Health, Education and Welfare, 1979b). This finding is consistent with data from Mexican treatment centers where 30.0% of all cannabis cases registered during the period 1970–1976 were daily users (Natera *et al.*, 1979). Another interesting finding is that younger users seem to be overrepresented in the drug centers' population when compared with the age group distribution of active users from the National Survey. The data for the general population of the U.S. for 1977, for example, indicate that current users aged 18–25 yr outnumber 2.1:1 those in the 12–17 age group. The drug centers' case registry for the same year shows a reverse tendency in this ratio; younger clients exceed older ones by 1.8:1. The Mexican treatment center data point in the same direction; users aged 18 or younger outnumbered older ones 1.2:1 among cases registered during the six-year period covered by the survey.

An additional difference between users in the general population and those registered in treatment centers concerns their distribution by sex. The 1977 National Survey in the U.S. established a male-female ratio of 1.5:1 for current users; the corresponding ratio for drug center cases admitted that year was 2.5:1. In Mexico, too, while surveys of general population samples conducted in several cities yield an average of 5.3 male users for each female (Medina-Mora and Terroba, 1979), this differential increases to a ratio of 11.4:1 among cases in treatment.

It is justifiable to consider cannabis users who are registered in treatment centers as "problem users." Only individuals who face difficulties could be expected to seek help. Thus, the preceding evidence suggests that personality deviance may not be the only factor that makes a problem user: the particular age and sex distribution that these users show as a group indicates that there may be social influences as well. Most individuals under the age of 18 yr are still living in their parental homes and attending school. They are more likely to enter treatment under the influence of external pressures than older users who have less contact with their families and have already left school. In fact, the U.S. statistics indicate that a sizeable percentage of drug treatment center clients had been referred there by either their school or their parents.

Parental or school pressures alone do not adequately explain why males are over-represented in the treatment center population. Some differences observed in patterns of usage may be relevant here. It has been asserted that, as is the case with alcohol (Ferrence, 1980), more males tend to consume cannabis (Ferrence and Whitehead, 1980). It is also likely that men are heavier users than women. If heavy usage increases the risk of experiencing difficulties, then males are more likely to fall within the problem-use category.

In conclusion, it may be stated that individual psychopathology is losing its importance as a determinant factor in the moderate use of cannabis. This is especially true in societies where the habit is becoming more prevalent and involving ever-growing sectors of the population. Psychopathology would appear to be related more to problem use, particularly if a deviant pattern of heavy consumption is involved. However, if problem use is defined in terms of the subject's involvement with treatment agencies, it is clear that, in addition to individual personality deviance, there are several social factors relevant to this definition.

3. ACUTE PSYCHOLOGICAL DISTURBANCE

It is generally agreed at the present time that cannabis is capable of causing some adverse psychological reactions during the course of its intoxicating effects. Paradoxically, this type of short-lasting disturbance has been more frequently documented in Western scientific literature than in parts of the world where the earlier reports on psychiatric complications of cannabis use originated.

Acute adverse reactions generally represent variations—in content and intensity—of the mood changes, trends of thought, and sensations which constitute the expected pharmacological effects of Δ^9–THC. It is not surprising that, in societies where the use of cannabis is a long established custom that individuals learn through traditional socialization, these deviant patterns of intoxication are less frequently observed. On the other hand, unpleasant experiences during cannabis intoxication could be expected to be more prevalent in societies where the habit has been only recently introduced, where there are many novice users, and where the effects of cannabis are still under close social and scientific scrutiny. Along these lines, the scientific literature originating from Western countries shows that acute adverse reactions to cannabis have more often been reported in the 1960s and early 1970s than in recent years. It would appear that there has been a progressive loss of interest in this particular problem on the part of health professionals, a diminishing tendency on the part of those affected to seek professional help, or, indeed, a decreasing incidence of those reactions in a cannabis-using population which is becoming more experienced.

Frequency

Early surveys showed consistently that acute psychological distress is not an uncommon occurrence during cannabis intoxication. Tart (1970) and Negrete (1974), inquiring among regular users, found that more than one in three of them admitted to having experienced symptoms of panic, paranoia, hallucinations, or unpleasant body distortion while inebriated by cannabis. These were self-selected and therefore possibly biased samples but other more strictly controlled samples also reported a high frequency of occurrence for these adverse reactions. Halikas *et al.* (1971) assert that 16 in a group of 100 regular users reported anxiety, fearfulness, sadness, despondency, aggressive urges, confusion, bewilderment, and auditory or visual hallucinations, as "usual" occurrences during intoxication. When the frequency of occurrence was classified as "occasional," these effects had been felt by a majority of the 100 subjects. Annis and Smart (1973) found that one out of five high school students who were involved in cannabis use had experienced unpleasant effects at least once; and that 2.6% of them had suffered adverse reactions seven times or more. Paranoid and panic reactions were found to have occurred in 15.5% of a group of stable, well-adjusted and moderate regular users (Marcus *et al.*, 1974). In a large sample of U.S. Army recruits, Patterson (1974) found 24.5% to be regular users of cannabis; 2.1% of these regular users reported having suffered at least one adverse reaction to the drug.

Adverse reactions have also been observed to develop in subjects undergoing laboratory experiments. These observations, made under controlled conditions in individuals whose mental status had been assessed prior to the experiment, add considerable weight to the conclusion that a state of acute psychological distress can be caused by cannabis. Melges (1976) elicited paranoid reactions in subjects to whom he had administered hashish; and Mendelson *et al.* (1972) reported one case of an acute panic reaction which developed in a casual user of marihuana during the first day of experimentation with the drug in their laboratory. One subject in a small experimental group, scheduled to smoke a rather heavy daily dosage of Δ^9–THC for a period of 28 days, became acutely paranoid and had to be withdrawn from the experiment before its completion (Frank *et al.*, 1976). Tassinari *et al.* (1973) used a much smaller dosage and observed, nevertheless, two cases of acute panic reaction in their group of 11 subjects.

When a comparison is made between the frequencies reported in these nonclinical populations with figures for cases treated in medical facilities, it becomes obvious that the great majority of individuals who suffer acute unpleasant reactions with cannabis either do not require or do not care to seek medical treatment. Pillard (1970) reports statistics from the student health clinic at a large university, where the use of cannabis was extensive. Acute adverse reactions amounted to no more than six cases per year for a population at risk of over 20,000. Lundberg *et al.* (1971) found only 10 acute cannabis reactions registered as primary diagnosis in more than 700,000 hospital admissions in an area of the U.S. where cannabis was being used extensively. From a population of 33,000 U.S. Armed Forces personnel in Europe, Tennant and Groesbeck (1972) identified only 18 acute panic or paranoid reactions due solely to cannabis which had been treated in the Forces' medical services over a period of several years. However, the incidence of these acute reactions was much higher among soldiers who were using other psychoactive drugs along with cannabis.

Of the 165 patients with a diagnosis of drug abuse admitted to

State Hospital in Brooklyn during 1968, 14 were cannabis cases and only seven of them were suffering from the type of reactions discussed in this section (Keup, 1970). A similar low incidence of treated cases is reported by Kroll (1975) among the U.S. Air Force troops stationed in Thailand during the period 1971–1972.

Clinical Manifestations

There have been several early attempts at classifying these acute adverse reactions on the basis of their different phenomenology and presentation (Weil, 1970; Negrete, 1973), but, as has been pointedly stated by Edwards (1976), it may be rather artificial to separate them into discrete clinical types. For even if there are some reactions in which panic, paranoid suspiciousness, suicidal urges or depersonalization constitutes the principal or sole feature, most cases present a fluid and unstable clinical picture containing a mixture of some or all of these manifestations.

Anxiety Reaction

The most common acute adverse reaction experienced with cannabis is a strong *anxiety* reaction, with panic and differing degrees of psychomotor agitation occurring in individuals who have not necessarily taken a heavy dose of Δ^9–THC, and whose sensorium does not appear altered. This kind of reaction reflects a rather idiosyncratic response to the drug and may be suitably described as a *pathological intoxication*. It usually lasts no longer than the period of time during which most cannabis smokers experience the subjective psychological effects of the drug (two to four hours). The subject is generally able to recall the experience with much objectivity (Klee, 1969; Halikas, 1974; Meyer, 1975; Granville-Grossman, 1979; Jones, 1980).

Acute Delirium

Another frequently reported reaction is a toxic confusional state, of the *delirium* type, which presents with symptoms of impaired cognitive functions, sensory perceptual distortions, memory loss, and fluctuating delusional formations. In addition, there can be psychomotor agitation and violent behavior. This reaction is dose-related and is included here because it, too, can be of a short duration. However, several reports describe it with a longer clinical course lasting up to a few days (Keup, 1970; Tennant, 1972).

Dysphoric Reaction

More recently, a new type of acute adverse effect of cannabis use has been reported. This is the so-called *dysphoric* reaction which develops as an untoward psychiatric side-effect during the course of Δ^9–THC therapy. Symptoms range from heavy sedation, catatonia-like immobility, and disorientation, to panic attacks, paranoid ideation, and hallucinations. This reaction is also dose-related, and has been observed to last for no more than a few hours. It subsides after discontinuation of the drug and supportive reassurance of the patient.

These dysphoric reactions have been observed during therapeutic trials with Δ^9–THC in psychiatric patients suffering from affective disorders (Kotin *et al.*, 1973; Ablon and Goodwin, 1974), and in cancer patients experiencing nausea caused by chemotherapy (Shiling *et al.*, 1980). The authors of the latter report remarked that these side-effects are more likely to develop in cannabis-naive patients who are unprepared to experience the mood-altering effects of the drug.

Etiopathology

Δ^9–THC *Action*

Many hypotheses concerning the causal mechanisms in these acute reactions have to do with the drug itself and its effects on the CNS. It has been well established now that different cannabis preparations present a wide variation in Δ^9–THC content. Ritzlin *et al.* (1979), for instance, found concentrations ranging from 1.5% to 19.1% of the total weight in street samples supplied by individuals who had experienced unpleasant effects from them. These authors were also able to assert that most street samples they analyzed were not contaminated with other psychoactive substances, i.e., that the reported reactions were caused by the cannabis alone. It is logical to assume that an individual accustomed to consuming low Δ^9–THC-content marihuana is likely to react adversely when using samples which could be more than 10 times stronger. Although the intoxicating effects of cannabis can include hallucinations, this only happens at dosages much higher than those habitually taken by the average user (Isbell *et al.*, 1967). It has been asserted that more naive users can develop a panic reaction when they experience such symptoms unexpectedly (Meyer, 1975).

Another possible causal factor cited is the route of intake. Weil (1970) suggests that toxic reactions are more likely to occur when Δ^9–THC is taken by mouth rather than inhaled. According to this author, cannabis smokers tend to regulate the progress of the intoxication, and are generally able to keep it at a desired level. Understandably, this type of control cannot be exercised when the drug is ingested. Laboratory experiments comparing the effects of Δ^9–THC under rapid and slow smoking conditions appear to lend support to this hypothesis: psychological changes are more noticeable when the individual has been forced to take the same total amount over a shorter period of time (Melges *et al.*, 1974). Petersen (1979) points out the influence that different inhalation patterns might have on the effects experienced by cannabis users. Individuals capable of collecting higher concentrations of Δ^9–THC at the alveolar level, and of holding the smoke there for a longer time, are more likely to feel the maximum psychoactive effects of the drug. The efficiency of pulmonary absorption has relevance not only to the understanding of the acute effects of the drug, but also to the possible long-term consequences of regular use.

Farber and Huertas (1976) and Payne and Brand (1975) observed six separate cases of severe intoxication in subjects who had injected aqueous extracts of cannabis i.v. The main symptoms were nausea, vomiting, hypotension, fever, renal failure, toxic hepatitis, and protracted muscular weakness, along with a remarkably mild mental reaction. Although the resulting severe physical syndrome may have overshadowed the psychological manifestations, it is probable that the toxic effects exhibited by these patients were due not to the central actions of Δ^9–THC but to microembolism caused by droplets of all the water-insoluble components of the injected concoction. In support of this interpretation is the evidence provided by the case of a man who had swallowed balloons containing hashish oil in order to smuggle the drug, and presented a picture consisting mainly of mental confusion when one of the balloons burst inside him (Lopez *et al.*, 1974).

Earlier contentions that acute adverse reactions to cannabis occur only when it is used concomitantly with other psychoactive substances (Weil, 1970; Tennant, 1972) can now be safely discarded. It has since been observed, time and again, that Δ^9–THC by itself is capable of inducing them. The present knowledge of the mechanisms by which these reactions are caused is rather limited. Paton (1973) hypothesizes that cannabis has mainly a disinhibiting action on the CNS: Δ^9–THC-induced impairment of transmitter output at the inhibitory synapses allows release (disinhibition) phenomena in the form of reverberatory discharges. Pointing to the well known alterations in time perception which occur during Δ^9–THC intoxication, this author suggests that sensory input is likely to be increased: the more stimuli individuals perceive, the more they will tend to overestimate the length of a given unit of time.

Research findings on the effects of Δ^9–THC on neurotransmitters—a subject of much importance to the understanding of the mechanism of its psychoactive functions—are still rather inconclusive and would appear, at this point, to be of limited clinical relevance. Δ^9–THC is believed to diminish central cholinergic activity (Revuelta *et* *al.*, 1979), and to be capable of altering the levels of biogenic amines in the CNS (Smith, 1980).

Melges *et al.* (1974) offer an interesting theory about the psychological mechanisms at work in the development of cannabis-induced paranoid reactions. These authors contend that disorganization in the temporal sequence of thinking caused by Δ^9–THC may result in alterations of thought content. Impairment in the rate, sequence, and goal-directedness of thinking upsets the regulatory feedback and feedforward mechanisms necessary for adequate testing of reality. During cannabis intoxication, subjects experience an intermittent loss of information about others' views of themselves; the lack of a firm point of reference allows for the amplification of unusual ideas subjects may have about self and others. In addition, the sense of time distortion caused by the drug leads to a telescoping of past, present, and future whereby unrelated events are connected only in each subject's peculiar "psychological" time. This phenomenon results in the loss of perceptive control and thus increases the intensity of apparent threats.

Individual Vulnerability

Even though the widespread occurrence of these adverse reactions would tend to suggest that individual predisposition is not an important factor (Edwards, 1976), it has been postulated that a degree of individual vulnerability is a prerequisite for their development. To some degree such a predisposition may consist of pre-existing psychopathology (Smith and Mehl, 1970; Negrete and Kwan, 1972), of maladaptive personality (Melges *et al.*, 1974; Naditch *et al.*, 1975), or of baseline neurophysiological malfunction (Campbell, 1971).

Reports of studies involving use of the Minnesota Multiphasic Personality Inventory (MMPI) assert that acute disorganization and panic are more likely to occur among individuals with certain specific personality profiles (Naditch *et al.*, 1975). Persons who score higher on the "schizophrenia" scale, as well as those showing patterns of rather primitive and regressive defense mechanisms, are believed to present a higher risk. On the other hand, well structured and more sophisticated defenses, of the type seen in paranoid personalities, are considered to be a safeguard against such toxic disorganization.

The individual's emotional state at the time of use is also thought to play a role in the occurrence of adverse reactions. Among those states of mind suggested as predisposing factors are ambivalence, active emotional distress, uninformed beliefs, and self-fulfilling prophecies (Weil, 1970; Negrete and Kwan, 1972; Naditch *et al.*, 1975).

Setting

Earlier analysis of the social dynamics of these adverse reactions placed considerable emphasis on the role of using cannabis in unfavorable settings. Since, in most parts of the world, cannabis is illegal and officially censured, its use calls for much trust in the environment and support among users. It has been suggested that even the presence of "disliked" persons may favor the development of unpleasant symptoms (Becker, 1953; Smith and Mehl, 1970; Weil, 1970).

Insufficient or misleading social indoctrination about the physical effects of the drug, and on the expected course of the intoxication, may account for the development of panic reactions among the more naive users (Becker, 1953). This assertion is supported by epidemiological evidence demonstrating that the bulk of cases registered with treatment agencies are in younger, less experienced users (U.S. Secretary of Health, Education and Welfare, 1979b). Although the available data do not specify the picture of the cannabis problems presented in these cases, it is only logical to assume that acute adverse reactions are included among them. It has been convincingly demonstrated by Naditch *et al.* (1975) that individual and environmental predisposing factors should not be separated in any analysis of their etiology. These authors concluded that, as far as their sample was concerned, neither setting nor set alone could satisfactorily explain the subjects' adverse experiences.

Some years ago, Becker (1953) predicted that as cannabis use became more widespread and socially acceptable, the frequency of these *pathological intoxications* would diminish. If the number of reports appearing in the scientific literature through the years can be considered an indicator, this prediction would seem to have been accurate. However, while the occurrence of panic reactions may have been favorably affected by changing social attitudes, it can be expected that the incidence of toxic delirium, which is dose-related, will continue to increase with the growing availability of cannabis preparations of high Δ^9–THC content, and the expansion in the numbers of heavy users.

4. RECURRENCE OF SYMPTOMS DURING DRUG-FREE PERIODS

Since it was first described by Keeler *et al.* (1968) and Weil (1970), the validity of this occurrence has been generally accepted by the scientific community. However, considerable effort is still needed in order to achieve a more precise phenomenological identification and to elucidate its etiopathology.

Keeler *et al.* (1968) reported four cases of individuals who, while in a drug-free state, reported experiencing sensations and psychological changes that they had felt previously while inebriated on cannabis. It is not clear, however, how long it had been since they had last taken the drug or, indeed, whether there had been a symptom-free period since that occasion. Wentworth-Rohr (1970) correctly points out that in order for these states to be called echo reactions or "flashbacks," there must be a spontaneous, drug-free, time-delayed, *re*appearance of disturbances previously experienced. He asserts that he was able to observe two such cases, both occurring at least three weeks after the last drug intake. Most other clinical reports available in the scientific literature are less precise about the timing of the recurrence of symptoms relative to drug use.

Unlike the acute panic and toxic reactions, or the acute paranoid psychosis, which have been observed to develop under experimental conditions, echo reactions have not been registered in laboratory studies as yet. Most descriptions originate from retrospective self-reports made by individuals who have sought help, or participated in questionnaire surveys. Such conditions render the validity of the data rather difficult to assess.

Users of psychodysleptic drugs, including those who take cannabis alone, are generally aware of the possible occurrence of flashback phenomena. Persons who could be suffering from disturbances not entirely related to cannabis may be inclined to interpret them as recurrences of symptoms induced by the drug, and report them as a flashback reaction. Pierce (1973) remarks that many such complaints involve symptoms only grossly similar to what the individual experienced during cannabis intoxication. Favazza (1973) correctly argues that subjects reporting flashbacks tend to be multiple-drug users and that they could only "think" that they know which drug in particular caused this reaction. He also cautions about the need to assess whether or not there has been a genuine discontinuation of use preceding the reappearance of symptoms.

Stanton and Bardoni (1972) surveyed drug use experiences in 2,256 American soldiers in Vietnam and found that 1.3% of all cannabis-only users responded affirmatively to the question: Have you ever had a flashback? The percentage was considerably higher for those using cannabis along with other psychoactive drugs. In a study of self-selected regular users in Canada (Negrete, 1974) positive answers were obtained from 60% of the sample. No doubt, sampling biases and the fact that it was up to the respondent to judge what was meant by a flashback experience, may have influenced these results. Nevertheless, it must be concluded that some kind of psychological alteration, judged by the users to be similar to the effects of cannabis, and occurring at some interval after drug intake, is not uncommon among users. If this is the case, then it must be concluded that most such experiences do not upset the individual enough to make him want to seek therapeutic intervention: the numbers recorded as clinical cases are much fewer than the survey figures would lead one to expect.

Pierce (1973) asserts that cannabis users are more likely to seek treatment for the recurrence of unpleasant symptoms than for sensations that do not disturb them. They may also report their symptoms when they become anxious about having lost voluntary control of their drug-related experiences, or because they find themselves unable to know just when these sensations will reappear. Another important motivation for disclosure is their anxiety about the meaning of such experiences (are they becoming mentally ill?).

Etiopathology

Not much has been firmly established at this point with regard to etiological factors and pathological mechanisms at play in these reactions. Anderson (1973) suggests that those users who smoke larger doses of cannabis are more likely to develop them. However, Stanton *et al.* (1976) assert that the representation of "habitual" users among the cases that they detected was comparable to that of lighter users. A common observation is that flashbacks are more likely to occur among multiple-drug users: in fact, Weil (1970) thought that they were only to be seen among cannabis smokers who had had previous LSD experiences. One of the two cases reported by Wentworth-Rohr (1970) was a subject whose echo reactions occurred when he had become intoxicated with alcohol.

Several authors contend that a most important causal factor is the subject's baseline degree of personality disturbance. Stanton (1973), for example, believes that ego functioning takes precedence over pharmacological action. Brown and Stickgold (1976), focusing on personality structure, point towards some traits (i.e., rigidity) which may contribute to rendering the individual anxious in respect to drug experiences. It is also well established that many individuals reporting flashback experiences have a previous history of psychiatric disorder (Negrete and Kwan, 1972; Brown and Stickgold, 1976), or are suffering active emotional disturbance at the time these episodes occur (Wentworth-Rohr, 1970).

A review of the evidence leads to the conclusion that flashbacks have been found to occur in the most varied circumstances: in individuals who had only one experience with cannabis and in regular users; among heavy and light smokers; among multiple-drug users and in cannabis-only users; and in persons showing different degrees of premorbid personality disturbance. There is an obvious need for controlled laboratory studies on the etiopathology of this condition.

5. CANNABIS PSYCHOSIS

The true existence of severe mental illness caused by cannabis, and extending beyond the period of acute intoxication, remains one of the most controversial issues in the discussion of the psychiatric complications of the use of this drug. It has become a cliché in the Western scientific community to assume that cannabis psychoses, if they exist, are more likely to be seen in North Africa, or in Asia, where patterns of heavy usage are more prevalent. This belief is supported by the fact that there is a strikingly higher frequency of hospital admissions for this diagnosis recorded in Morocco and India than in the industrialized countries of the West. In general, the available evidence thus far is so uncertain that some authors after reviewing it have concluded that the case for cannabis psychosis, as a discrete clinical entity, has yet to be made (Murphy, 1963; Edwards, 1976).

Phenomenology

Two rather different types of cannabis-induced psychotic symptomatology have been described: one involving impairment of consciousness, orientation, and memory, in addition to the distortions in sensory perception and thinking; another in which thought pathology occurs without noticeable alterations in cognitive functions. It would seem clear that the confusional form has been more universally observed and that it is the one whose validity is less disputed at the time of this writing.

Taking note of the many reports made over the years of alleged cannabis psychosis, it is possible to distinguish at least four separate clinical conditions:

(i) a psychotic state of the acute brain syndrome type;

(ii) a schizophrenia-like acute psychosis without mental confusion;

(iii) a protracted psychotic illness featuring cognitive deficit, along with paranoid and/or affective symptoms;

(iv) a variety of psychotic manifestations developing as withdrawal reactions.

Acute Brain Syndrome

The acute confusional syndrome presents with impairment of sensorium and recent memory; visual and auditory hallucinations; proprioceptive distortions; persecutory feelings and other delusional formations; emotional lability; and bouts of aggressive, impulsive, and regressive behavior. This picture has been observed in public mental hospital patients in India (Chopra and Smith, 1974) and in the Bahamas (Spencer, 1970), in American military personnel in Vietnam (Talbott and Teague, 1969) and in Europe (Tennant, 1972). It is said to develop among individuals who take heavy doses of cannabis on a daily basis for a prolonged period of time. The onset is sudden rather than insidious, and the response to therapy very favorable. There appears to be a wide discrepancy between the American Forces cases and the mental hospital patients with regard to the course and the duration of the psychotic state. The soldiers are reported to have recovered enough to resume normal activities within 3–11 days, whereas the others stayed in hospital for periods of up to four weeks. These papers do not provide sufficient information to allow one to ascertain whether this difference is due to the illness itself or to such factors as premorbid personality, treatment resources, and social support conditions.

Schizophreniform Psychosis

The schizophreniform syndrome, a form of psychosis also thought to develop after chronic and heavy cannabis use, is characterized mainly by paranoid thinking, perception of the environment as hostile, delusions of persecution, ideas of reference, body image distortions, auditory and visual hallucinations, occasional violent behavior, and wide variations in mood. All this occurs against a background of clear consciousness, preserved memory, and unaltered cognitive functions. The stream of thought, however, does not show some of the most typical features of schizophrenia. There is no blocking, loosening of associations, overinclusiveness, or tangential answering. Insight appears fairly well-preserved and recovery occurs within a short time. Bromberg (1939) describes a few such cases in New York. Chopra and Smith (1974) found a sizeable number among mental hospital patients in Calcutta. Thacore and Shukla (1976) are convinced that this is the most common type of cannabis psychosis to be found in their region of India, and Asuni (1964) observed 11 cases of a schizophreniform illness among the 16 cannabis patients admitted to a mental hospital in Nigeria in 1962.

Both Bromberg (1968) and Chopra and Smith (1974) stress the premorbid psychopathology involved in the development of this condition. Thacore and Shukla (1976), on the contrary, assert that they found no evidence of previous psychiatric disturbance among their cases.

Understandably, many objections have been raised against the diagnostic criteria applied in these cases. Some authors think that there is no way to distinguish these psychoses from psychogenic ones which occur without the contribution of cannabis (Varma, 1972). Others feel the specificity of this psychosis could be confirmed only after proper follow-up, an aspect rather frequently neglected in the case reports. Murphy (1963), for example, remarked that 15 of the 21 cannabis psychoses reported by Bromberg (1939) had been re-diagnosed as chronic schizophrenias or affective disorders within two years of their discharge from hospital.

A further element of contention is the fact that several authors, particularly in non-Western societies, appear to make a diagnosis of cannabis psychosis mainly on the basis of a history of cannabis use and the relatively fast improvement exhibited by these patients. Porot (1942) even suggests that many cannabis psychoses could be mis-diagnosed as schizophrenia because psychiatrists neglect to notice the acute course of the illness. These diagnostic criteria cannot be accepted nowadays as it is well known that there are psychogenic psychoses which also present a short-term favorable evolution.

Chronic Psychosis

The protracted psychotic illness resulting from chronic cannabis abuse has been described as a mixture of the most diverse phenomenology: self-neglect, absentmindedness and lethargy, periods of psychomotor excitement and violent behavior, disorientation with respect to time, delusions of persecution and of grandeur, impoverishment of intellectual functions, and memory deficit—these symptoms are said to follow a recurring course over a period of months or years. Christozov (1965) made a most detailed description of this condition based on 140 cases treated at the Berrechid Mental Hospital in Morocco. Chopra *et al.* (1942) analyzed the characteristics of "chronic" cannabis psychosis and stressed the resemblance they have to "dementia and mania." Long-lasting mental symptoms were also reported in two Nigerian children who had been given intoxicating doses of cannabis (Binitie, 1975).

If the validity of this diagnosis is accepted, then satisfactory reasons must be found to explain the prolonged course of this form of toxic psychosis. Most of these reports are based on retrospective studies of mental hospital records. Little is said in them about treatment facilities or the rehabilitation resources available to the patients; it is likely that some psychoses, which might otherwise evolve towards a quick recovery, would persist for a longer time in an institution with inadequate facilities. Mikuriya (1968) visited Morocco and remarked that many of these patients while in hospital were seldom seen by medical staff; that their diagnosis had been made without adequate information; and that standard neurological and physiological tests had not been performed. Another important factor is the social background of these patients: most are described as destitute and derelict, frequently living on skid row (or its equivalent) with no family ties or means of support. The prolonged stay in hospital may have been as much due to these adverse social conditions as to the illness itself. Moreover, there might be other poverty-related illnesses involved. Murphy (1963) pertinently remarks that it is difficult to distinguish the cannabis psychosis described in Morocco from similar states associated with chronic malnutrition and endemic infection.

Continuing use of the drug is another possible cause for the chronic recurrent course shown by these patients. One would expect them to abstain while in hospital but, as occurs with alcoholics elsewhere, cannabis abusers may find ways of obtaining the drug even in confinement. Continuing use of cannabis was the main cause found by Davison and Wilson (1972) for the relapses and prolongation of a psychotic condition they treated in England.

An additional and certainly important factor could be the existence of a primary chronic psychogenic psychosis in which cannabis use is only an associated feature. This possibility is apparent in the report by Davison and Wilson (1972) who remark that their patient's cognitive and thought disturbance symptoms cleared but that he was still showing some "residual" affective deficit one year after cessation of cannabis use. A similar finding was described by Spencer (1970) among cases in the Bahamas.

Withdrawal Reactions

Laboratory studies have established beyond doubt that withdrawal of cannabis after frequent and heavy use is capable of inducing both subjective discomfort and observable clinical manifestations. Jones and Benowitz (1976), in a well controlled study with human subjects, observed withdrawal symptoms which started some 12 hr after cessation of use, reached their peak at the 30-hr mark, and had almost disappeared 90 hr later. The subjects exhibited irritability, restlessness, insomnia, and anorexia, as well as a general "influenza-like" state with sweating and rhinorrhea. EEG recordings showed short-term rebound REM hyperactivity, but a few subjects continued to report disturbed sleep for weeks after the experiment. No psychotic symptoms were elicited and it is said that this clinical picture resembles the one which follows cessation of benzodiazepine use. A similar active but non-psychotic symptomatology was observed by Bensusan (1971) in a group of users who ran out of cannabis while traveling through a South African desert.

In spite of the lack of supporting data, it may be pertinent to mention here some clinical reports of an alleged psychosis related to cannabis withdrawal. Fraser (1949) observed nine cases of psychotic behavior lasting three to six weeks in army recruits who had had their supplies discontinued; Schweitzer and Levin (1976) describe a *delirium tremens*-like condition which developed in a heavy cannabis user after he was admitted to hospital because of an accident; and Teitel (1977) reports he has seen in his private practice three cases of "manic depressive" symptoms following withdrawal. The reader is left with serious doubts about the validity of these findings. The prolonged psychosis described by Fraser is clearly in discordance with the withdrawal states observed under controlled experimental conditions. Although Schweitzer and Levin assert that the delirium they observed was somewhat different from that caused by alcoholic withdrawal, they nevertheless mention that the patient disclosed daily use of beer and rum. The affective disorders mentioned by Teitel cannot be properly assessed, as he gives no information about his patients' patterns of cannabis use, or about the course followed by the disease.

In conclusion, there appears to be considerable agreement on the existence of a relatively short-lasting (a few days to four weeks) psychosis featuring thought disturbance, transient cognitive and memory deficit, poor impulse control, and regressive behavior, which develops in the course of prolonged and heavy cannabis use. It is also clear that it affects only a selective minority of users and that intervening factors, other than the drug itself, are not yet well known. The specificity of the schizophreniform syndrome, of the severe withdrawal states, and of the chronic psychosis, has not yet been satisfactorily demonstrated.

6. EFFECTS ON INDEPENDENT PSYCHIATRIC ILLNESS

Given the fact that Δ^9–THC is a drug with well established effects on mood, sensory perception, and thought processes, its interaction with active psychiatric illness seems to have been accorded surprisingly little attention. It has been frequently said that cannabis can precipitate or trigger an overt psychotic state in individuals in whom the condition was only latent. It is also reasonable to expect that a drug with psychodysleptic effects may cause transient psychotic decompensation in borderline personalities. Although it has not been specifically researched, this particular interaction between cannabis and pre-existing psychopathologies became evident during experimental studies (Frank *et al.*, 1976). Furthermore, a sizeable number of cases admitted with the diagnosis of "cannabis psychosis" has been identified as presenting "schizoid" premorbid personalities (Chopra and Smith, 1974). Tennant and Groesbeck (1972) noted that the rate of schizophrenia diagnosed among American Army personnel in Europe grew from 1/1,000 to 38/1,000 between 1967 and 1971, and interpreted this tendency on the basis of the increase in cannabis use. It is, of course, exceedingly difficult to demonstrate that a given psychosis would not have become manifest without the use of cannabis. This is one of the major obstacles hampering research on this problem.

Two hypotheses which have not yet been properly tested are that the use of cannabis may have prevented the inception of overt psychiatric illness in individuals who remain nonpsychotic in spite of high risk factors in their background, and that cannabis may have helped some users achieve a better emotional adjustment and a higher level of social performance (Grinspoon, 1970–1971; Smith and Mehl, 1970; Beaubrun and Knight, 1973).

An important issue still largely neglected is that of the possible changes that cannabis may introduce in the phenomenological presentation of psychiatric disorders. With such a large sector of the general population involved with cannabis, it is legitimate to assume that a sizeable number of individuals suffering from psychiatric disorders is included among the users. But only seldom is detailed information about cannabis use recorded in the clinical histories of psychiatric patients.

Nevertheless, there are already several reports in the literature that are likely to stimulate research in this problem in the near future. Treffert (1978) mentions four cases of schizophrenia whose clinical course, he is convinced, was adversely affected by the use of cannabis. These patients showed a favorable therapeutic response in abstinence and relapsed each time they resumed use of the drug. The author cautions that many schizophrenics may tend to smoke cannabis during their convalescence in order to cope with the postpsychotic depression frequently experienced by them, or as a way of re-activating their social life. Davison and Wilson (1972) noted that the schizophrenia-like symptomatology in their young male patient worsened after weekend leaves when he would indulge in cannabis smoking.

It has also been proposed that cannabis use may interfere with the proper identification of psychotic illness. Harding and Knight (1973), for instance, describe the case of four individuals who were diagnosed as paranoid schizophrenics on admission, but became clearly manic three to four days later. These were heavy cannabis users, and the authors believe that the thought disorder, social withdrawal, echolalia, echopraxia, and hallucinations, which they exhibited at the beginning, were toxic effects of Δ^9–THC. The more specific manifestations of the basic affective disorder they suffered became evident only upon withdrawal from the drug. Interestingly, it was also noted that these patients did not show clouding of sensorium or memory deficit, as could be expected in cases of toxic psychosis. The authors contend that the hyperalertness of the manic state may have overshadowed these symptoms.

Other reports stress the unusual degree of violent, aggressive, and destructive behavior observed among psychotic patients who use cannabis. Bernhardson and Gunne (1972) have seen it in a sample of schizophrenic and manic cases in Sweden; and El-Guebaly (1975), from Canada, asserts that Δ^9–THC renders manic-depressive patients "more aggressive and paranoid."

Epilepsy is another illness of which the clinical manifestations are also believed to be susceptible to the influence of cannabis. In spite of contradictory results yielded by animal studies, clinical studies with human subjects tend to confirm the convulsive potential of the cannabinoids. Keeler and Reifler (1967) reported the occurrence of *grand mal* convulsions subsequent to marihuana use, and some of the epileptic patients surveyed by Feeney (1976) believed that cannabis was capable of causing their attacks. A very carefully conducted experiment on the effects of cannabidiol on EEG activity in an epileptic patient clearly demonstrated that increases in the blood levels of the drug correlated positively with increases in epileptic discharges (Perez-Reyes and Wingfield, 1974). It is believed that the activating effects shown by Δ^9–THC on certain types of epilepsy may be due to its anticholinergic action (Feeney *et al.*, 1976).

Patients suffering from endogenous depressive illness have shown particularly negative responses to Δ^9–THC. A majority of the subjects involved in two separate double-blind therapeutic trials with the drug had to be withdrawn on account of severe "dysphoric" reactions (Kotin *et al.*, 1973; Ablon and Goodwin, 1974). The patients were naive about the drug and, given the prerequisites of the study's design, could not be adequately prepared to anticipate the effects of a mood-altering substance. These factors may account for the panic reactions and paranoid feelings they exhibited. Nevertheless, it was also observed that the occurrence of these symptoms was significantly more frequent among patients with unipolar depression than in those showing a bipolar course. This finding suggests that dysphoric effects may be related to particular psychopathologies, in addition to set and setting. Δ^9–THC demonstrated no significant antidepressant action in the patients able to complete the trial.

There have been a few reports on cases of mutism as a consequence of acute cannabis intoxication (Marcotte, 1972). However, it is not clear from those case studies whether the patients were unable to speak because of a conversion reaction, dissociative crisis, or a severe case of dysarthria.

Apart from comments on the predisposing role of neurotic disturbances on adverse reaction to cannabis, the literature reports no specific findings on the interaction between cannabis and neurotic illnesses. Many clinicians have learned that cannabis is sometimes used as a sedative or hypnotic by chronically anxious or phobic patients. However, these are only anecdotal reports and not the result of research studies on the subject.

Little is known, too, about the possible interference of cannabis with the pharmacological actions of prescribed psychotropic medication, another question of obvious relevance to the understanding of its interaction with mental illness. A recent case report suggests, for example, that cannabis is capable of interfering with lithium treatment. A patient's serum lithium concentration, which was normally stable within a therapeutic range, tended to reach toxic levels after he began using marihuana on a daily basis (Ratey *et al.*, 1981).

The need for more research with a view to measuring the effects of cannabis on independently occurring psychiatric disorders is obvious. Clinicians need adequate information to be able to advise their patients on the consequences of initiating or continuing with the use of cannabis while suffering from a psychotic or neurotic illness.

7. NONPSYCHOTIC CHRONIC EFFECTS

Amotivational Syndrome

On the basis of clinical observations, McGlothlin and West (1968) asserted that continuing heavy exposure to cannabis may render users apathetic; reduce their drive and ambition; and diminish their capacity to carry out complex tasks, pursue long-term plans, follow routines, endure frustration, perform effectively in what they undertake to do, and master new learning. Other reports described chronic users as neglectful of their personal appearance, sluggish in their mental responses, and emotionally dulled (Kolansky and Moore, 1975). Regular users are also said to exhibit short attention and concentration spans, distractability, fragmentation in the flow of thought, magical thinking, diminished communication skills, and poor judgment (Malcolm, 1976).

These rather detailed descriptions reflect the opinion of highly trained clinicians, but it would seem permissible to equate them with traditional observations made in Morocco and in Eastern societies (Bell, 1972; Sharma, 1975; Edwards, 1976) where the "kif-happy" vagabond and the hashish-using beggar have long been known to show indolence and overall personality impoverishment.

It is rather difficult to identify the type of problem that is being alluded to in the concept of "amotivational" syndrome. The features included in the preceding clinical descriptions could be interpreted as manifestations of particular philosophical attitudes, of some kind of psychological deficit or, simply, of chronic physical fatigue. The confusion permeates most writings on the subject. Not surprisingly, the most diverse approaches have been utilized in attempting to test the validity of this clinical condition. In some studies, school marks and drop-out rates have been used as indicators; in others, work record and capacity for physical effort; yet others have focused on performance of psychophysiological tests. The results have so far been inconclusive.

Mellinger *et al.* (1976) compared groups of college students with different patterns of drug use on the basis of their academic transcripts and history of dropping out. He found that twice as many cannabis-only users as nonusers had left school before completion. The percentage of school abandonment among multiple-drug users was much higher and it is well known that the heavier cannabis smokers are individuals who use other drugs as well. Also, drug users in general tended to obtain lower marks. Mellinger and coworkers concluded that, if students who are "non-committed" to attending college are excluded from the comparison, then the differences in marks and drop-out rates between users and nonusers disappear. But it could be argued that his conclusion is based on a circular reasoning: an attitude of noncommitment may very well be the result of drug-induced amotivation.

Campbell (1976) observed that 77% of heavily smoking college students had lower marks in the second half of the school year; the corresponding percentage of light users was much lower, but still well above the tendency for the general student body. He also undertook to review papers handed in by heavy cannabis smokers at different times during the academic session: his conclusion is that they manifested a growing inability to synthesize and enunciate abstract concepts as the year progressed. Brill and Christie (1974), on the other hand, found no difference in school performance among students with drug patterns ranging from abstinence to regular use.

Studies conducted in Greece (Boulougouris *et al.*, 1976) and in Costa Rica (Carter and Doughty, 1976), comparing the work records of heavy users with matched controls, reached opposite conclusions. In the Greek sample, users were more frequently unemployed and had a higher rate of job changes than their controls. This finding was interpreted as a possible manifestation of poor motivation to work. Users in the Costa Rican study showed similar work histories; however, the heaviest users, who would be expected to be most affected, were thought to exhibit adequate motivation because they recorded the highest incomes, the least unemployment, and the most material possessions of the entire user group. The conclusions of both these studies are questionable. The cannabis-using subjects selected in Greece clearly showed indications of being more sociopathic than the controls; consequently, they could be expected to have poorer work records even without the cannabis involvement. Many of the Costa Rican users admitted to trading in cannabis—certainly a way of being productive with regard to earning money, but which does not rule out decreased motivation to engage in regular work.

Comitas (1976) asserts that his findings in a study of field laborers in Jamaica clearly refute the concept of an amotivational syndrome. The subjects were engaged in sugar cane cutting, a type of work which allows accurate quantification of production. The figures showed no significant differences between ganja smokers and controls in total weight of cane cut. However, it was observed that many users would "perform better" at work if intoxicated. That is, they experienced the need to smoke during their heavy labor and this could be interpreted as state dependency, developing as a consequence of poor motivation to work. Furthermore, sugar cane cutting is a kind of work that may attract people who are less inclined to pursue regular activities. It is seasonal and generally paid on the basis of daily production, and would not seem appropriate for testing an individual's capacity for sustaining long-term effort. Another field study conducted in Jamaica (Schaeffer, 1975), this time measuring the work output of a different type of agricultural worker, arrived at the conclusion that heavy cannabis users do show lower productivity over a period of time. No differences were found, however, between moderate users and nonusers.

Important additional observations were made during the course of laboratory experiments in North America. Subjects were kept in residence and put on a régime of heavy daily use. They were also required to work at assigned tasks in order to earn the means to pay for their daily nonessential items. A lethargic attitude developed progressively during the course of the study but it was demonstrated that it could be altered with appropriate incentives. In spite of the declining level of activity displayed by these subjects, they continued to perform the tasks which they were being paid for (Miles *et al.*, 1972; Lessin and Thomas, 1976).

In conclusion, it would seem logical to assume that individuals who use heavy doses of cannabis on a daily basis may remain somewhat lethargic and uninterested in events and activities not closely related to their immediate personal needs. However, this alteration has not yet been satisfactorily demonstrated through quantitative measurements. Moreover, the improvement in overall performance that may follow cessation of use has not been adequately studied. These issues remain unresolved at the present time.

Residual Psychological Deficit

It is a well known fact that cannabis impairs the test performance of human subjects during acute intoxication. Whether long-term exposure to the drug causes a more permanent or cumulative deficit has not yet been established.

Psychological deficit has been found among chronic users in Egypt, India, and Greece. Soueif (1976) maintains that there are significant differences between heavy hashish users and nonusing controls in a number of tests which explore the level of cognitive function. His results indicate that the poorer performance displayed by users becomes more noticeable when the comparison is made between the better educated individuals who live in urban settings. Mendhiratta *et al.* (1978) tested daily users of high average intake and found that they showed decreased speed and accuracy, longer reaction time, and lower scores on the Bender-Gestalt test than the matched controls. Stefanis *et al.* (1976) observed that, although the total WAIS I.Q. score averages did not show a significant difference between controls and chronic hashish users, the latter performed significantly worse in the comprehension, similarities, and digit-symbol substitution subtests. Several factors qualify the validity of these findings. In order to obtain meaningful results with most of the tests utilized in these studies, the subjects must possess a minimum degree of sophistication. These tests involve handling of words, figures, abstract geometric shapes and, most important, the use of paper and pencil. Individuals whose formal educational training is minimal, whose occupation has for the most part been manual labor, and who belong to a social class where verbal communication is restricted to a limited vocabulary, can be expected to show a "floor" effect in such procedures. The comparability of users and controls with respect to the skills needed to complete these tests does not appear to have been adequately ensured, e.g., matching on the basis of gross categories such as literacy vs. illiteracy. Moreover, questions could be raised also with respect to the influence that alcohol abuse may have had on the results, e.g., 18% of the users in the Greek study were found to have enlarged livers.

Most other studies, performed in industrial societies, in Jamaica, and in Costa Rica, have yielded no significant differences between users and controls. Grant *et al.* (1973) tested medical students; Bruhn and Maage (1975), a group of long-term users who were serving prison sentences; Carlin and Trupin (1977), a small group of daily users. Important doubts can be raised as to how representative these samples were of chronic heavy users at large. However, the more carefully designed studies of Bowman and Pihl (1973), Knights and Grenier (1976), and Satz *et al.* (1976), have also failed to elicit differences. With so many negative results originating from separate studies, it would appear obvious that cannabis-caused cognitive deficit, if it exists, is not a universal phenomenon. The evidence available at the present time does not allow for definitive conclusions. One need only think what would happen if chronic alcohol drinkers were tested by the same procedures—certainly a majority of them would show no indications of deficit. Does this mean that alcohol causes no cognitive impairment at all?

Brain Damage

The state of the evidence at the present time does not permit one either to conclude that cannabis produces structural brain damage or to rule it out. The report of Campbell *et al.* (1971) on findings of cerebral atrophy in heavy smokers has been rightly questioned on the grounds that the investigators were basing their conclusions on a procedure of low reliability—the pneumoencephalogram; that the subjects were multiple-drug users; and that there were no controls for comparison. In addition, two separate studies in which computerized tomography was employed have failed to elicit significant differences between users and controls (Co *et al.*, 1977; Kuehnle *et al.*, 1977).

Research on its effects on EEG clearly indicates that cannabis is capable of causing noticeable changes in brain physiology. Users have been found to show either higher or lower percentages of alpha-components than nonusers, and to have higher or lower visual evoked response amplitudes (Richmon *et al.*, 1974). Heath (1972) observed EEG recordings in one human subject with implanted electrodes and concluded that cannabis causes acute changes in the form of slow-wave, high-amplitude activity. He repeated his observations, implanting electrodes in six Rhesus monkeys and found that the subcortical changes lasted well beyond an eight-month period of Δ^9-THC inhalation (Heath, 1976).

This study has been criticized on the ground that unusually high doses were given, although Heath *et al.* (1980) subsequently demonstrated that the doses used produced THC blood levels that were equivalent to those induced in human subjects who smoked an "average-size joint."

Subjects in a 94-day cannabis study (Cohen, 1976) also showed lasting EEG changes. The abnormalities were significantly more marked in subjects who had taken heavier doses, but it was observed that even in abstinence, cannabis users had more EEG irregularities than nonusing controls. It is not known yet how long after cessation of use the EEG changes persist. Also, it has been reported that chronic users develop tolerance to some of the EEG changes caused by cannabis (Feinberg *et al.*, 1975).

The most convincing evidence on brain damage would come from postmortem studies but this type of information, so far, is not available.

Effects on Psychosocial Adjustment

In the past, there was much concern about the possibility that cannabis use may lead to multiple-drug abuse; by and large, those fears have not been confirmed. It is a well established fact that heavier users are more likely than moderate ones to be users of other drugs, but the role of cannabis as a stepping-stone towards generalization of addictive behavior has not been proven (Le Dain, 1972). Very recent evidence, however, suggests that this issue may become a matter of concern again. The 1979 U.S. National Survey of Marijuana Use has found that 12- and 13-yr-old youngsters who use cannabis are more likely to start drinking alcohol at that early age as well (Petersen, 1980). The simultaneous daily administration of both Δ^9–THC and ethanol increases the rate and magnitude of tolerance development towards the effects of the latter (Siemens, 1978); this laboratory finding suggests that regular cannabis users may develop a capacity to drink larger amounts of alcohol and, in that sense, cannabis could prove capable of altering drinking behavior. Another interesting observation is that Δ^9–THC has been found effective in the control of morphine-like withdrawal symptoms in laboratory animals (Zaluzny *et al.*, 1979); but whether or not this phenomenon may influence the drug-seeking behavior of individuals who use cannabis and opiates conjointly has not yet been established empirically.

Another matter of concern has been the possibility that regular use of cannabis may lead to a life of crime. The evidence available on the association between cannabis, crime, and violence, has been thoroughly reviewed by Abel (1977), who concludes that marihuana use does not precipitate violence in the majority of those using it either sporadically or chronically. No doubt, its relatively weaker dependence liability and readier availability are factors which prevent the occurrence of the type of antisocial behavior generally associated with drugs eliciting marked dependence. Nevertheless it has been observed that cannabis, like other intoxicating agents, may facilitate the expression of violent behavior in certain vulnerable individuals, e.g., temporal lobe epileptics, particularly when it is used in certain settings that tend to precipitate such behavior.

Another effect of cannabis relevant to the area of social adjustment is its impairment of the user's ability to drive a motor vehicle. Simulation experiments have established beyond question that cannabis, particularly when taken along with alcohol, increases the risk of accidents; but the number of field surveys dealing with this problem is still limited (see Klonoff, this volume). No doubt, the difficulties encountered in attempts to obtain readings of blood Δ^9–THC levels in the field are responsible for the paucity of studies in this area.

A causal association between regular use of cannabis and chronic emotional instability has not been proven (Jessor, 1979), but it is pertinent to mention here the findings of the 1979 U.S. National Survey in which only 5% of the 18- to 25-yr-old respondents stated that they believed cannabis had "no bad effects" on the psychological status of the user. In addition, Brill and Christie (1974) reported that in a sample of university students, 2% of all cannabis users decided to quit because of negative effects on their emotional adjustment, and that long-term users, particularly those taking larger amounts, rated their emotional state at the time of the enquiry as being significantly worse than that of lighter users and nonusers. This latter finding, however, was to be expected as it is well known that heavier patterns of use are usually shown by individuals who are primarily emotionally unstable.

The increase in frequency of use among students suggests the possibility that many of them attend classes while under the influence of cannabis. Since memory and cognitive ability are directly impaired by acute use of the drug (Ferraro, 1980), it can be expected that this practice may seriously diminish the quality of their academic work. Furthermore, experiments in laboratory animals have demonstrated that the administration of Δ^9–THC is capable of causing an impairment in learning which persists for a long time after the drug has been discontinued (Fehr *et al.*, 1976; Radouco-Thomas *et al.*, 1976). The implications of these findings are serious indeed and need extensive exploration.

Recent evidence also alerts one to some additional effects of cannabis which could potentially affect general emotional and social adjustment. The reported actions of cannabis on reproductive function, including inhibition of LH-releasing factor (LHRF) with subsequent depression of gonadotrophin levels, lowering of testosterone blood levels, and increase in the proportion of anovulatory menstrual cycles in female users (reviewed by Hembree *et al.*, 1976; Nahas, 1979), all point towards the possibility that cannabis consumption may seriously affect physical development and psychological maturation in users of puberal age. Moreover, the consistent results from laboratory studies showing that Δ^9–THC and its metabolites are capable of crossing the placental barrier, and that they can be detected in the milk of lactating mothers (reviewed by Harclerode, 1980), raise the question of early cannabis interference with psychological development. [*Editors' note*: for a more detailed review of these questions, see Bloch, this volume.] Early results from a prospective study of cannabis-using women clearly indicate that babies born to those smoking five or more marihuana cigarettes per week exhibit clinically detectable signs of CNS effects. Tremors, high-pitched cry, and increased startle response were observed at assessment nine days postdelivery; and other manifestations such as decreased ability to habituate to light were still present 30 days after birth (Fried, 1980).

8. CONCLUSIONS AND RECOMMENDATIONS

There seems to have been a decline in interest in the psychiatric aspects of cannabis research in recent years. This tendency may be due to the low frequency of cases seen in clinical facilities (in spite of the constant growth in the population of users), to the difficulties encountered in arriving at definitive conclusions with human research methods currently in use, and to an attitude of complacency which the scientific community might have developed as a consequence of the increasing social acceptance of cannabis use.

Epidemiological trends indicate that this habit has extended well beyond the limits of selective and deviant minorities, particularly in the industrialized societies of the West. This tendency suggests that individual psychopathology is becoming less significant as a factor in determining cannabis consumption. Comparative studies, however, still detect higher degrees of psychological deviance in heavy users. Patterns of heavy use are also over-represented in populations registered with helping agencies. In addition to the modest efforts made so far in this area, there is a pressing need for valid and reliable clinical criteria, as opposed to "social" ones, for defining "problem" users for purposes of pertinent psychiatric action.

Acute panic and paranoid states are the most commonly observed short-term adverse psychological effects of cannabis use. The validity of these conditions is no longer questioned, as they have been seen both in clinical settings and in laboratory experiments. Although the diminishing frequency of clinical reports of this type of reaction tends to support early contentions that they may be due mainly to adverse social conditions and the user's lack of experience, it has now been satisfactorily demonstrated that setting alone does not explain their occurrence. Additional work is needed to identify the intervening pharmacological, neurophysiological, and psychopathological factors.

Other acute reactions of increasing clinical relevance are some severe dysphoric states which have been observed to occur during the course of Δ^9–THC therapy. A concerted effort must be made to develop specific treatment procedures with a view to preventing or minimizing these untoward psychiatric side-effects.

Most of the evidence available on the recurrence of drug symptoms during abstinence (flashbacks) originates from self-report answers to rather imprecise questionnaire surveys, and from subjective descriptions given by individuals who believe they have experienced them. The systematic phenomenological analysis of this clinical condition has been largely neglected, and controlled studies of the intervening etiopathogenic factors do not yet appear to have been carried out.

The only picture of a specific cannabis psychosis now supported by sufficient evidence is a short-term condition—from a few days to four weeks—with symptoms of mental confusion, memory impairment, regressive and impulsive behavior, delusional formations, and sensory-perceptive distortions. Its frequency of occurrence in Western societies is very low, and it seems to affect mainly very heavy users. A commonly found predisposing factor is a high degree of premorbid personality disturbance. The incidence of this condition can be expected to rise along with the general increase in numbers of daily or more frequent users in the population. More research is needed to identify risk factors other than excessive use.

A highly relevant area of research in which current data are clearly too limited is that of the influence of cannabis on independently occurring psychiatric illness. The evidence already available, however, is sufficient to warrant large-scale studies on the effects of cannabis on the phenomenology of some of the most prevalent psychiatric disorders, in terms of both symptomatology and evolution. Also, specific research is urgently needed on the interaction between cannabis and chemical agents commonly used in psychiatric pharmacotherapy, including its possible influence on therapeutic response.

The data from studies that have tested the validity of the "amotivational syndrome" concept are inconsistent, and do not permit the draw-ing of definitive conclusions. In some of the best known studies the subjects' capacity to engage in physical labor has been used as an indicator of this phenomenon. There are some signs that this may not have been the most suitable choice. Laboratory findings have shown that tolerance to the motor effects of Δ^9–THC develops with continuing use. Moreover, individuals who appeared increasingly lethargic after a period of heavy daily intake, proved to be capable of mobilizing themselves to perform tasks for which they were paid. It would seem that drug-induced indolence can be modified by an appropriate incentive.

Most studies that have compared the performances of chronic users and controls on psychophysiological tests have failed to elicit significant differences. It is evident that gross cognitive deficit is not a common effect of chronic use. However, if cognitive deficit caused by alcohol is taken as an example, it is clear that studies on relatively small samples, such as are at the moment available for cannabis, cannot be expected to rule out the possibility of such a deficit in some users. Furthermore, the instruments utilized in these studies require a certain level of sophistication in the subjects. The groups tested—mostly peasants and poorly educated urban dwellers—may have shown a "floor" effect which would have masked the finer differences between users and nonusers.

The question of cannabis brain lesions is likely to remain unanswered until adequate postmortem studies are conducted. These are not now available.

Given the recent findings on cannabis effects on reproductive functions and on long-term impairment of learning abilities, research is also warranted on possible consequences for the physical development, psychological maturation, and overall quality of academic achievement of young users. In addition, the experimental findings that Δ^9–THC and its metabolites cross the placental barrier and can be detected in the milk of lactating mothers make it imperative to learn how to identify early signs of developmental deficit in the offspring of cannabis-using women.

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Cannabis Tolerance and Dependence

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1. INTRODUCTION AND DEFINITIONS

In discussions of tolerance or dependence, definitions are important. Imprecise use of these terms has led to misunderstanding of the phenomena, and their possible mechanisms and health implications.

Tolerance

In this review I use the term tolerance to mean a diminished drug effect following repeated doses, or the need for greater doses to maintain an effect. It assumes a return of the lost drug effect if the dose is increased. A rough subclassification used in this review consists of: dispositional, metabolic, functional, and behavioral tolerance. Clearly, these terms contain certain implicit assumptions about the mechanisms involved.

Cannabis researchers, like other drug researchers, use a variety of terms to describe tolerance. A partial list includes: acquired, acute, behavioral, behaviorally augmented, biochemical, cellular, central nervous system, dispositional, functional, learned, innate, metabolic, organic, peripheral, pharmacological, physiological, psychological, real, reverse, and tissue. The choice of terminology used to describe findings often reflects the theoretical background and biases of the researcher. One consequence of such imaginative terminology is that sometimes mechanisms are implied by the terminology or are assumed without adequate consideration of alternative explanations.

The term tolerance, of course, simply describes a phenomenon. It has no implications regarding mechanisms. Many or most of the terms listed above refer to very similar processes and maybe common mechan-

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isms. Some evidence for this was covered in a classic review by Kalant *et al.* (1971).

Dependence

Varied definitions of dependence have contributed to even more misunderstandings. I use the term to mean the appearance of fairly predictable (but dose- and time-related) signs, symptoms and behaviors when drug administration is suddenly stopped or the dose is decreased. The signs and symptoms decrease or disappear when the drug is restarted or when a pharmacologically similar drug is administered. Dependence, as used here, does not imply nor is it synonymous with addiction, increased drug-seeking, craving, or other behaviors that may have some relationship to dependence. Drug self-administration and related behaviors are also determined by environmental, personality, genetic, social, and unknown factors, in addition to whatever the contribution of dependence might be (Wikler and Essig, 1970; Wikler, 1976; Sellers, 1978; Jaffe, 1980).

Psychological and Physiological Dependence

Many prefer to make a distinction between physical and psychological dependence. If physiological or biochemical abstinence phenomena are measurable, the organism is said to be physically dependent. If behavioral or subjective changes or drug-seeking behavior follows drug cessation unaccompanied by physiological, abstinence signs, the organism is said to be psychologically dependent. That distinction is more in the tradition of mind-body dualism than in keeping with contemporary models of how the soma and psyche may interact. With a drug like cannabis, many of the abstinence phenomena are subtle or even psychological or, at the very least, less dramatic than the severe delirium tremens that may be associated with alcohol dependence or the intense opiate withdrawal symptoms that might follow interruption of a sustained daily dose of 100 mg or more of morphine. Scientists sometimes find only what they are looking for. If one has a definition of dependence modeled after *severe* alcohol or opiate dependence, then other manifestations of dependence are easily overlooked. This has happened in some cannabis studies.

American Psychiatric Association Definition

In the United States attempts have recently been made to redefine cannabis dependence in the American Psychiatric Association *Diagnostic and Statistical Manual* (DSM III) (American Psychiatric Association, 1980). That definition is based on a pattern which may include difficulty in reducing or stopping use, repeated unsuccessful efforts to control consumption, periods of temporary abstinence or restriction of use, intoxication throughout the day, use of cannabis nearly every day for at least a month, two or more episodes of cannabis-related delusional disorders, and impairment in general functioning. A related element required for the diagnosis of dependence is tolerance, characterized by a need to use increasing doses of cannabis to maintain the desired effects (American Psychiatric Association, 1980).

The American Psychiatric Association's diagnostic criteria are based more on clinical experience and judgment than on hard, numerical data about consequences, and include a number of concepts that are difficult to define operationally. It tends to confound tolerance, drug-seeking, and acute effects and puts little emphasis on withdrawal phenomena. That some of the criteria may be clinically useful is illustrated by a recent clinical report of cannabis dependence (Weller and Halikas, 1980).

Relationship between Tolerance and Dependence

In theory, it would be unusual for a drug not to be associated with dependence if significant tolerance develops (Seevers and Deneau, 1963; Solomon, 1980). For many psychoactive drugs, the mechanisms of tolerance and dependence seem to be intimately related (Kalant *et al.*, 1971; Jaffe, 1980). Thus, odds are in favor of finding dependence if tolerance is marked, *assuming the phenomenon is properly looked for under appropriate conditions.* As with tolerance, the intensity and manifestations of dependence are determined by many factors including dose, schedule of drug administration, past drug and behavioral history, genetics, species differences, and the biological systems, behaviors, or symptoms studied. For any drug, the time of onset and intensity of withdrawal phenomena depend on the elimination kinetics of the drug and its active metabolites, particularly the rate of clearance from the body (Boisse and Okamoto, 1978; Sellers, 1978). In general, drugs with half-lives longer than 35 to 40 hr do not produce an intense withdrawal syndrome. These considerations are particularly important in relation to cannabis. Since the metabolism of cannabinoids is particularly complex with the production of many metabolites according to nonlinear kinetics (Hunt and Jones, 1980), one might expect complexity in characterizing dependence.

Organization and Emphasis in This Working Paper

Since the ARF/WHO study focuses on health and behavioral consequences, my emphasis is on data from human studies, such as they are. Because of the difficulties in achieving optimal conditions for human studies, so that tolerance and dependence can be arranged in an experimental, controlled environment, we are necessarily dependent on animal experiments. These I will review, less completely or thoroughly. I have tried to err on the side of over-inclusiveness in bibliographic references for those who might want to pursue specialized areas in more detail. Some are referred to only in the Tables but not in the text.

The review generally covers the literature up to late 1980, with some deliberate omissions of repetitive articles (or ones I could not understand). Other omissions are accidental. One of the unsettling things about discussing tolerance is that it must be considered in almost every study—certainly in any experiment involving more than a *single* dose—if one is to be certain of covering all the possibilities. Because issues related to dependence are more controversial, I have tried to emphasize them. Thus, tolerance is less comprehensively covered, in a vain attempt to keep this discussion short.

2. TOLERANCE: GENERAL OVERVIEW

Literally hundreds of published reports are directly concerned with tolerance and probably a thousand more are indirectly relevant. Table 1 gives a selective overview. I will not try to review them all.

Reviews

Excellent reviews that are still reasonably up-to-date exist and offer tabular listings by species, effects, etc., for those who want specific information. A comprehensive general review containing 375 references has large sections on tolerance (Harris *et al.*, 1977). A briefer review describes what Harris (1978) terms a "remarkable degree of tolerance to THC and other psychoactive cannabinoids." Reports that focus on the behavioral pharmacology of Δ^9-tetrahydrocannabinol (THC) and, hence, emphasize what is termed by some "behavioral" tolerance, include good reviews of many of the obvious pitfalls that make the pharmacology of THC difficult to study (McMillan, 1977; Meyer, 1978). A review focusing on behavioral and EEG correlates emphasizes the role of behavior and learning in the development of tolerance (Fried, 1977). A comprehensive review of both tolerance and dependence by Wikler, one of the pioneers in this area, includes 84 references covering the literature to the mid-1970s (Wikler, 1976).

General Characteristics: Animal Studies

General descriptions of cannabis tolerance as reflected in the reviews (and in my opinion) lead to the conclusions summarized below. There is surprisingly little disagreement among reviewers as to the main characteristics. Table 1 continues and updates a summary table of animal studies presented in the review by Harris *et al.* (1977). This

TABLE 1

Effects of THC to which Tolerance Develops in Animals

Species	Substance	Effect	Reference
Frog	Δ^9–THC	Rapid loss of righting reflex and inhibition of leg withdrawal. Not metabolic	Abel, 1973
Pigeon	Δ^9–THC	Tolerance to behavioral effects without pharmacokinetic changes	Dewey *et al.*, 1976a
Pigeon	Δ^9–THC and 11–OH–Δ^9–THC	Operant behavior. Rapid tolerance and cross-tolerance	Ford and McMillan, 1971
Chicken	Δ^9–THC	Rapid tolerance to hypothermia, more so in older birds	Abel *et al.*, 1973
Chicken	Δ^9–THC	Rapid tolerance to behavioral and hypothermic effects in neonates	Abel *et al.*, 1972
Mouse	Δ^9–THC	Rapid but varied with parameter studied. On 2nd dose lasted to 19 days	Anderson *et al.*, 1975
Mouse	Cannabis extract	Not tolerant to reduction in activity. Oral doses	Cutler *et al.*, 1975
Mouse	Δ^9–THC	Calcium stimulation of phosphodiesterase absent after 28-day treatment	Dolby and Kleinsmith, 1977
Mouse	Δ^9–THC	Anticonvulsant	Karler *et al.*, 1974
Mouse	Δ^9–THC	Hyperthermia, not metabolic	Lawrence and Pertwee, 1973
Mouse	Δ^8–THC	Immunosuppressant effects	Loveless and Munson, 1976

TABLE 1 (CONTINUED)

Species	Substance	Effect	Reference
Mouse	Δ^9–THC	Brain tissue respiration	Nazar *et al.*, 1974
Mouse	Δ^9–THC	Corticosterone levels	Pertwee, 1974
Mouse	Δ^9–THC	Stimulation, less to depression	Radouco-Thomas *et al.*, 1976
Mouse	Δ^9–THC	To hypothermia, but no tolerance to aggression	Ten Ham and De Jong, 1974
Mouse	Δ^8–THC	To hypothermia, but no tolerance to aggression	Ten Ham and van Noordwijk, 1973
Rat	Δ^9–THC	Weight change, temperature and motor activity in 7–14 days. No tolerance to pressor response	Adams *et al.*, 1976
Rat	Cannabis extract	To depressant effects in 10 days, then increased irritability and killing with continued treatment	Alves and Carlini, 1973
Rat	Δ^9–THC	To depressed activity then increased activity. Neurochemical correlates	Aulakh *et al.*, 1980
Rat	Δ^9–THC	More in younger animals	Barnes and Fried, 1974
Rat	Δ^9–THC	Lever press rate on complex reinforcement schedule	Boren and Rhodus, 1974
Rat	Δ^9–THC	Learning enhanced rapid tolerance	Carder and Olson, 1972
Rat	Cannabis extract	Tolerance to behavioral effects, not to aggression	Carlini, 1968

TABLE 1 (CONTINUED)

Species	Substance	Effect	Reference
Rat	Cannabis extract	No tolerance to enhanced fighting behavior	Carlini and Masur, 1969
Rat	Δ^9–THC	Decreased locomotor activity, rapid tolerance, biphasic pattern	Davis *et al.*, 1972
Rat	Δ^9–THC	Inconclusive support for metabolic mechanism. Cross-tolerance with phenobarbital	Davis and Borgen, 1975
Rat	DMHP and Δ^8–THC	Conditioned avoidance, single dose tolerance	Delini-Stula, 1973
Rat	DMHP	Prolongation of hexobarbital sleeping	Delini-Stula, 1973
Rat	Δ^9–THC	Complex interactions	Drewnowski and Grinker, 1978
Rat	Δ^9–THC	Food intake inhibition and to hypothermia in 11 days	Fernandes *et al.*, 1971
Rat	THC and crude cannabis extract	CBD alters hepatic microsomes more than THC	Fernandes *et al.*, 1973
Rat	Δ^9–THC and 11–OH–Δ^9–THC	Rapid behavioral effects	Ford *et al.*, 1976
Rat	Δ^8–THC	Dose-related, to behavioral effects	Frankenheim, 1974
Rat	Δ^9–THC	Response latency	Fried and Husband, 1973
Rat	Δ^9–THC	Anticonvulsant effects	Fried and McIntyre, 1973

TABLE 1 (CONTINUED)

Species	Substance	Effect	Reference
Rat	Δ^9–THC	Behavioral and anticonvulsant activity	Fried and McIntyre, 1973
Rat	Δ^9–THC	Ataxia and vocalization	Fried and McIntyre, 1973
Rat	Cannabis and Δ^9–THC	Cross-tolerance between smoked and injected THC on behavior	Fried, 1976a
Rat	Δ^9–THC	Prenatal exposure increased time for tolerance	Fried, 1976b
Rat	Δ^9–THC	Brain serotonin levels increased without tolerance	Ghosh and Poddar, 1974
Rat	Δ^9–THC	Depended on pharmacological and behavioral factors	Glick and Milloy, 1972
Rat	Δ^9–THC	Decreased testicular weight after 10-day treatment	Goldstein *et al.*, 1977
Rat	Δ^9–THC	Only minimal behavioral testing	Hine *et al.*, 1977
Rat	Δ^9–THC	Limited tolerance to drug discrimination	Hirschhorn and Rosecrans, 1974
Rat	Δ^9–THC	Increased hepatic microsomal activity	Ho *et al.*, 1973
Rat	Δ^9–THC	Learning to perform under influence essential	Järbe, 1978
Rat	Δ^9–THC	Behavioral	Johansson *et al.*, 1974
Rat	Δ^9–THC	Partially maintained for 10 days off drug	Johansson *et al.*, 1975

TABLE 1 (CONTINUED)

Species	Substance	Effect	Reference
Rat	Δ^9–THC	No tolerance to bradycardia	Kaymakçalan and Sivil, 1974
Rat	Δ^9–THC	Tolerance and dependence	Kaymakçalan *et al.*, 1977
Rat	Δ^9–THC	Rapid acquisition and loss, considered mix of metabolic, functional, and behavioral	Larsen and Pryor, 1977
Rat	Δ^9–THC	Oral, no change in pentylenetetrazol or audiogenic seizure thresholds after withdrawal	Leite and Carlini, 1974
Rat	Δ^9–THC	No tolerance to blood pressure drop in hypertensive rats	Lewis *et al.*, 1974
Rat	Δ^9–THC	Hypothermia	Lomax, 1971
Rat	Δ^9–THC	Partial tolerance to some neurochemical changes	Luthra and Rosenkrantz, 1974
Rat	Δ^9–THC	Increased brain metabolism to account for behavioral tolerance	Magour *et al.*, 1976, 1977
Rat	Δ^9–THC	No tolerance to decreased food intake	Manning *et al.*, 1971
Rat	Δ^9–THC	No tolerance	Manno *et al.*, 1978
Rat	Δ^9–THC	Decreased defecation	Masur *et al.*, 1971

TABLE 1 (CONTINUED)

Species	Substance	Effect	Reference
Rat	Δ^9–THC	Bar pressing for water in 2–3 days	Masur, 1973
Rat	Δ^9–THC	Varied tolerance to behavioral effects, not to neurochemical ones	Miczek, 1979
Rat	Δ^9–THC	Varied tolerance to behavioral effects, not to neurochemical ones	Miczek and Dixit, 1980
Rat	Δ^9–THC	Hypotensive effects in hypertensive rats	Nahas *et al.*, 1973
Rat	Δ^9–THC	EEG and certain nonconditioned behaviors	Pirch *et al.*, 1972a and b
Rat	Marihuana extract and Δ^9–THC	Decreased EEG voltages	Pirch *et al.*, 1972a and b, 1973
Rat	Δ^9–THC	Disruptive effects on open field behavior, balance beam, and a swimming test	Potvin and Fried, 1972
Rat	Δ^9–THC	Prolongation of hexobarbital sleeping	Rating *et al.*, 1972
Rat	Δ^9–THC	Hypothermia	Rating *et al.*, 1972
Rat	Δ^9–THC	Many effects via smoked route	Rosenkrantz and Braude, 1976
Rat	Δ^9–THC	Tolerance not metabolic	Siemens and Kalant, 1974
Rat	Δ^9–THC	Long-lasting (4-week) tolerance to many effects	Singh and Das, 1977

TABLE 1 (CONTINUED)

Species	Substance	Effect	Reference
Rat	Δ^9–THC Δ^8–THC	Little tolerance to exploratory behavior, low doses	Sjödén *et al.*, 1973
Rat	Δ^9–THC	No tolerance to decreased eating	Sofia and Barry, 1974
Gerbil (epileptic)	Δ^9–THC	Anticonvulsant effects	Ten Ham *et al.*, 1975
Rabbit	Synthetic cannabinoids	No tolerance to intraocular pressure drop after daily treatments for 1 year	Green *et al.*, 1977
Rabbit	Δ^9–THC	Prior adaptation to chamber determines pattern of tolerance	Martin and Consroe, 1978
Cat	Δ^9–THC	Biphasic and complicated tolerance pattern. Some EEG changes back to baseline levels after 30 days of treatment, others persist	Barratt and Adams, 1972
Dog	Δ^9–THC	Behavioral without pharmacokinetic changes. Decreased radioactivity in synaptic vesicles	Dewey *et al.*, 1976a and b
Dog	Δ^9–THC	Some cardiovascular effects, not others	Jandhyala and Buckley, 1977
Dog	Δ^9–THC	Some cardiovascular effects, not others	Jandhyala, 1978
Dog	Δ^9–THC	Static ataxia, not metabolic	Martin *et al.*, 1976
Dog	9–nor–Δ^8–THC	Static ataxia	Martin *et al.*, 1976

TABLE 1 (CONTINUED)

Species	Substance	Effect	Reference
Primate	Δ^9–THC	Rapid to behavioral effects	Adams and Barratt, 1974
Primate	Δ^9–THC	Sleep EEG, no tolerance or rebound	Adams and Barratt, 1975a
Primate	Cannabis extract	Behavioral effects, slowly with oral doses but increased aggression	Chapman *et al.*, 1979
Primate	Δ^9–THC	Tolerance and dependence	Deneau and Kaymakçalan, 1971
Primate	Δ^9–THC	Faster to effects important to the animal	Elsmore, 1975, 1976
Primate	Δ^9–THC	Decreased accuracy and amount of responding on DRL schedule for food	Ferraro and Grilly, 1972, 1973, 1974
Primate	Δ^9–THC	Decreased accuracy and amount of responding on DRL schedule for food	Ferraro and Grisham, 1972
Primate	Δ^9–THC	Decreased response rate on a DRL schedule	Harris *et al.*, 1972
Primate	Δ^9–THC	Many acute effects during pregnancy but maternal behavior altered	Kaplan, 1979
Primate	Δ^9–THC	Spaced responding, acquired faster if during intoxication	Manning, 1973, 1976a and b

review is a useful start for those who want to read the details that led to the following conclusions.

Tolerance to both behavioral and physiological effects can develop to a marked degree (at least 6,000-fold increase in dose requirement) exceeding the level generally seen with opiates (McMillan *et al.*, 1970, 1971, 1972). Cannabis tolerance is found in all species adequately studied. The rapidity and magnitude of tolerance cannot be accounted for by metabolic (i.e., dispositional) mechanisms. It can develop very rapidly with relatively infrequent dose administration. A number of investigators have demonstrated tolerance after a single dose of THC on some measures—a few examples are hypothermia in the rat (Lomax, 1971) and mouse (Uran *et al.*, 1980) and righting reflex in the frog (Abel, 1973). Generally, exposure over three to six consecutive days is enough to produce tolerance in animals or humans. The duration of tolerance seems more variable. Duration varies with measure and species; tolerance can last for months, although in humans and some animal experiments a substantial degree of tolerance can be lost 24 hr after the end of chronic administration. Tolerance may develop more rapidly in younger animals. Cross-tolerance develops between cannabis and alcohol, barbiturates and morphine, though asymmetrically on some measures. The development of tolerance in certain circumstances can be facilitated by what seems to be a learning process, although it can also occur without any need for the animal to learn or respond under the drug's influence.

Although degree of tolerance varies, there is no cannabis effect to which some degree of tolerance does not develop when tested under proper conditions. A caveat regarding this claim is that tolerance develops so rapidly that on occasion adaptive responses to the presence of cannabis are probably already included in the initial measurement of direct effects of the drug. Tolerance does not develop to such adaptive changes. The diversity of the adaptive changes, even after one or two doses of THC or cannabis, is such that a simple, single mechanism of tolerance is unlikely to be apparent soon.

Tolerance results in an increase in the frequency of some behaviors and a decrease in the frequency of others. Similarly, some physiological and neurochemical processes may be increased and others decreased, though again it is not always clear what is a direct effect of the drug and what is a rapid adaptation to its presence.

The tolerance literature suffers from a relative absence of systematic experimental replication. It is not so much that people are unable to replicate each other's work, but rather that they do not try.

Tolerance: Human Studies— Mostly with Cannabis That Is Smoked

Recognition of tolerance to cannabis in humans has come slowly. Statements to the effect that cannabis-induced "tolerance and physical dependence do not occur" were common in standard pharmacology textbooks well into the mid-1970s (Goldstein *et al.*, 1974). The United States National Commission on Marihuana and Drug Abuse, when discussing the "addiction potential" of marihuana, concluded that "fact and fancy have become irrationally mixed regarding marihuana's physiological and psychological properties. Marihuana clearly is not in the same category as heroin insofar as its physiological and psychological effects are concerned. In a word, cannabis does not lead to physical dependence" (National Commission on Marihuana and Drug Abuse, 1972). In a book describing an extensive marihuana study in which experienced users smoked up to 20 one gram cigarettes per day for a 21-day period, it was concluded that the heaviest users did not become tolerant to the subjective effects of marihuana even though they did rapidly develop some tolerance to various physiological effects (Mendelson *et al.*, 1974a). Yet the animal literature from the same period (Table 1) described tolerance to cannabis and THC that was characterized by rapid development, large magnitude, and wide generality (see, for example, Lomax, 1971; McMillan *et al.*, 1971; Paton *et al.*, 1973). Wikler, in a comprehensive review of various aspects of cannabis tolerance and dependence, concluded, as did other reviewers (Paton, 1973; Paton *et al.*, 1973), that the evidence indicated that both tolerance and dependence can develop in humans (Wikler, 1976).

Older Literature

Despite very clear data from animal studies and older research in humans, many scientists, nonscientists, and marihuana users in the mid-1970s believed that tolerance did not develop to cannabis (Edwards, 1968). The reasons for this great discrepancy are not clear. Probably because of relatively infrequent use of cannabis of fairly low potency, tolerance was not, in fact, commonly observed among users in the United States in the 1970s or recognized by the users themselves. During the early 1970s there was what bordered on an unreasonable distrust of the older cannabis literature. That older literature suggested, both on the basis of clinical observation and by reasonably well controlled laboratory studies, that with increased levels of use diminished cannabis effects were commonly observed (Mayor's Committee, 1944a; Williams *et al.*, 1946). In those controlled studies done during the early 1940s, nonusers of cannabis were generally more affected than users as reflected by behavioral, psychological, and subjective indices, and decreased effects followed sustained intoxication in both groups. True, these findings are only evident if one reads the detailed results of the research. In the summary statements of the Mayor's Committee (1944a), it was said that "if tolerance is acquired, this is of a very limited degree." Such summary statements seem to get quoted more in the cannabis literature than the experimental details do.

In those reports and in others of that era, opiates were used as a model for most discussions of addiction and tolerance and thus perhaps the cannabis situation was assessed from a wrong perspective. It is easy to forget that in the early 1940s there was still disagreement among scientists as to whether nonopiate drugs such as alcohol or barbiturates could produce "true" physiological dependence and addiction. The disagreement subsided only in the late 1940s and early 1950s when definitive experimental laboratory studies established the occurrence of dependence on these drugs to everyone's satisfaction (Isbell *et al.*, 1950, 1955; Wikler and Essig, 1970).

Observations of Users

More recent indirect evidence suggesting development of tolerance to cannabis comes from naturalistic observations. American soldiers in Germany smoked doses of up to 20 g per day of hashish (Tennant and Groesbeck, 1972); Jamaican laborers, 24 g of high potency hashish daily (Bowman and Pihl, 1973); and Greek users took similarly high doses (Dornbush, 1974; Boulougouris *et al.*, 1976; Stefanis *et al.*, 1976a). If potent hashish is assumed to contain 5%–10% THC, the daily consumption of THC can apparently range up to 2,400 mg/day in these users. If one extrapolates from the profound effects of a 70 mg oral dose of THC (Tassinari *et al.*, 1976) or a 20 or 30 mg smoked dose when given to the chronic marihuana users often tested in laboratory sessions in the United States (Jones, 1973), one must assume that some degree of tolerance has developed to allow these overseas users to take such enormous daily doses without suffering incapacitating toxicity.

Laboratory Studies: User vs Nonuser Comparisons

In a host of laboratory studies in recent years, cannabis users with some degree of experience with the drug, when given acute single doses of cannabis, showed fewer and less intense physiological changes, and less impairment on performance and behavioral tasks, than did less frequent and less experienced users (Mayor's Committee, 1944b; Jones, 1971; Meyer *et al.*, 1971; Cohen and Rickles, 1974; Fink, 1976; Fink *et al.*, 1976; Volavka *et al.*, 1977). Data from similar studies with what appear to be equally good controls, however, indicated no difference in marihuana or THC effects when given to populations of frequent and infrequent users (Casswell and Marks, 1973; Cappell and Pliner, 1974; Milstein *et al.*, 1974, 1975a and b; Perez-Reyes *et al.*, 1974, 1976;

Casswell, 1975). In fact, some investigators observed what they thought to be evidence for increased sensitivity to THC or cannabis effects in frequent users (Weil *et al.*, 1968; Lemberger *et al.*, 1971b; MacCannell *et al.*, 1977). However, definitions of a frequent user vary greatly in these papers, and the apparently conflicting findings might reflect nonequivalence of the subjects in different studies.

Moreover, in most of those early studies, such indirect evidence of tolerance development could be explained by alternate hypotheses, including personality or genetic differences, use of drugs other than cannabis, innate differences in drug metabolism, cannabis that was less potent than expected, motivational differences, etc. Considering the rapidity with which tolerance can be lost in humans (Jones *et al.*, 1981), a few days of abstinence could make a user resemble a nonuser on some measures. The best way to study the development of tolerance to cannabis or THC experimentally, is to administer the substances repeatedly to an individual and to observe the results at various times during the course of the drug administration.

Studies in Controlled Environments

Williams et al. *Public Health Service Studies:* In one of the first studies of volunteers living on a closed ward, Williams *et al.* (1946) noted a gradual disappearance of the cannabis-induced increases in heart rate observed on the initial administration, and a gradual lessening of subjective effects, as subjects smoked up to 24 g a day of cannabis (as 9 to 26 cigarettes daily, M = 17) over a 39-day period. Although the marihuana could not at that time be assayed for THC content, it was judged by the volunteers as being of good quality. The subjects gradually increased their self-selected dosage over the 39-day smoking period. Although they showed some tolerance to the cardiovascular effects and to some of the subjective effects, other responses to the drug were unchanged. For example, throughout the smoking period, patients seemed less motivated to engage in hobbies and other activity than before smoking. Body weight increased about 2 kg during the smoking period, and there was a small increase in plasma volume. When the smoking stopped, a sudden loss occurred over a few days that returned the weights to presmoking levels.

Similar but greater changes followed in another group of patients given oral doses of pyrahexyl, a THC-like synthetic drug, over a 28-day period in amounts of up to 1,600 mg per day. If this dose is roughly equivalent to 500 mg of THC, then the average amount of pyrahexyl absorbed was much lower than the amount absorbed when 500 mg THC is smoked, assuming that the bioavailability figures of Ohlsson *et al.* (1980) are correct. Over the course of the experiment the pulse rate increase observed initially was followed by a return to baseline levels, and then by a fall below the predrug level. A pattern of weight gain during administration and then sudden weight loss on cessation of the pyrahexyl was also evident. Sleep time increased initially on drug and decreased upon drug withdrawal. Other changes on drug withdrawal will be mentioned later when dependence is discussed.

McLean Hospital/Boston: In similarly designed but more elegantly instrumented studies in the early 1970s, with measured and assayed cannabis, similar patterns of change were evident in volunteer subjects smoking up to 22 cigarettes daily while living on a research ward for 21 days (Mendelson *et al.*, 1974a and b, 1976a, b, c; Babor *et al.*, 1975).

UCLA: In a study in which lower doses of smoked cannabis (M = 5 cigarettes daily) but a longer period of smoking (64 days) were employed, a similar pattern of modest tolerance to cardiovascular changes and to subjective changes gradually developed (Nowlan and Cohen, 1977), as did tolerance to initial respiratory depressant effects (Bellville *et al.*, 1976).

Chicago: Relatively minimal tolerance developed to cardiovascular effects of smoking marihuana through a spirometer system daily for 10 days (Renault *et al.*, 1974). The variability in response suggests that the investigators did not have good control over THC delivery. Therefore, it is difficult to judge just what occurred in this study.

Columbia/New York City: A group of six hospitalized volunteers smoking about 15 one-gram marihuana cigarettes daily for a 28-day period showed a pattern of gradually developing tolerance (Georgotas and Zeidenberg, 1979).

Canadian Studies: A Canadian study involved 20 regular users smoking relatively low doses (up to 30 mg THC/day) for up to 48 days. Drug-treated subjects showed less tachycardia when challenged with 30 mg THC after 30 days of smoking than did subjects challenged with 6 mg who had smoked placebo for the 30-day period (Gibbins *et al.*, 1976). This greater tolerance was maintained when both groups were given 30 mg THC.

Outpatient Repeat Dose Studies

A few outpatient studies suggest that long periods of cannabis smoking are unnecessary if sensitive and well-designed measures of tolerance are used. With outpatient volunteers, usually marihuana users, what has been termed “acute” (i.e., rapidly developing tolerance) has been repeatedly observed. In five outpatient subjects smoking two marihuana cigarettes containing about 14 mg THC daily, tolerance developed to the initially intense euphoric effects, memory impairment, and increased cardiac rate as well as to the initial increase of activity in the alpha band of the EEG (Dornbush *et al.*, 1972). Barratt *et al.* (1974) had 12 subjects smoking a similar dose over a 10-day period and noted tolerance to the initial depression of rapid eye movement sleep. Five occasional cannabis users smoked a single marihuana cigarette twice weekly for three months and were tested on a battery of cognitive and motor tests. Tolerance developed to changes in heart rate and the subjective symptoms (Borg *et al.*, 1975). Rapid tolerance to impairment of performance on a complex reaction time task was seen during a daily four-session test series in which 18 subjects smoked a single cigarette each day (Peeke *et al.*, 1976). No tolerance to cardiovascular and autonomic effects developed. In comparison, outpatients given oral 20 mg THC doses for four consecutive days showed only slight evidence of tolerance (Hollister and Tinklenberg, 1973).

Behavioral Tolerance

It has become a tradition when reviewing cannabis research to discuss separately something called "behavioral tolerance." I think this is all right if we realize what we are doing and do not muddle conceptual issues. Many investigators of behavioral tolerance either implicitly or explicitly distinguish between what is often termed pharmacodynamic mechanisms of tolerance, based on cellular adaptations (functional tolerance), and learned or behavioral tolerance (Manning *et al.*, 1971; Ten Ham, 1977). In a simple description of results, this conceptual confusion can be ignored, but ultimately it must be dealt with when conclusions are drawn and new experiments are designed. It should be possible to consider drug-behavior-environment interactions and still assume that mechanisms occurring at the cellular level are equally important and ultimately must be understood to account for both so-called "learned" and "pharmacodynamic" tolerance. Of course, one could assume that learning has no underlying biological mechanisms and thus, in effect, separate the mind from the body. A good case for not doing this has been made by many other reviewers of issues relating to cannabis tolerance (Kalant *et al.*, 1971; Fried, 1977; McMillan, 1977). The suggestion that both learned and pharmacodynamic tolerance are merely different reflections of the same underlying mechanisms seems the most parsimonious, yet hypotheses are posed and experiments designed as if they were quite different phenomena.

As might be expected, there is more variability in the tolerance developing to the behavioral effects of cannabis than to effects measured by most physiological and many biochemical indices. This should not be surprising, since even simple behaviors are determined by the interaction of many biological and nonbiological factors. The influence of these factors makes for even more complex drug/environment/learning interactions with repeated drug administration than may be the case in biological systems that are not affected by these factors (Glick and Milloy, 1972). Ferraro (1976), for example, presents a comprehensive behavioral model of marihuana tolerance, but in his theorizing and model building, he, as do many behavioral researchers (Solomon, 1980), pays only lip service to what he terms pharmacodynamic factors. The predictions from his model have utility. The first prediction is that behavioral tolerance to marihuana is more likely to develop if the drug initially produces adverse effects on behavior-environment relationships. If marihuana produces behavioral changes that do not have adverse environmental consequences, then tolerance is less likely to develop or will appear more slowly. In studies with chimpanzees (Ferraro and Grilly, 1973, 1974), with squirrel monkeys and with rats (Manning, 1976a and b), tolerance was best seen when behavioral effects of THC were detrimental to the animal, i.e., when increased shocks were experienced after THC was given, or loss of positive reinforcement occurred, the animal rapidly developed tolerance. When THC acted to decrease the number of shocks, animals developed little or no tolerance.

A second prediction is that behavioral tolerance is more likely to develop if the occurrence of tolerance in itself does not produce adverse effects on behavior-environmental relationships. For example, when the animal must discriminate between the drug and nondrug states in order to obtain positive reinforcement, tolerance to the stimulus properties of cannabis is very slowly acquired and minimal, even though tolerance to other drug effects may develop rapidly (Bueno and Carlini, 1972; Hirschhorn and Rosecrans, 1974).

A third prediction is that behavioral tolerance is more likely to develop under simple than under complex behavioral tasks. There is extensive evidence that tolerance develops to different behaviors at different rates within the same animal in one experiment. Different schedules of reinforcement produce different rates of tolerance development (Ferraro and Grisham, 1972; Harris *et al.*, 1972; Elsmore, 1975; Vandell and Ferraro, 1976) with the simple tasks usually showing faster tolerance than the complex.

The fourth prediction is that behavioral tolerance is more likely to develop rapidly if the opportunity to respond under the influence of marihuana is present. Various paradigms have been used to demonstrate this principle, and they generally involve comparing the performance of two groups of animals given a test dose of cannabis after several days of chronic exposure during which one group is treated before the daily task performance, and the second is given an identical dose immediately after (Carder and Olson, 1972; Ferraro and Grilly, 1974; Olson and Carder, 1974). It is the relative rate of tolerance development which is affected (Järbe, 1978), and probably the best way to conceptualize the phenomenon is to consider it a variation of what has been termed behaviorally augmented tolerance with equal exposure to the task (LeBlanc *et al.*, 1975). Tests with rats (Ten Ham, 1977) and humans (Peeke *et al.*, 1976) show that learning while not intoxicated can induce what appears to be the same amount of tolerance as does learning during cannabis exposure. Tolerance certainly can develop without behavioral testing (Potvin and Fried, 1972; Hine *et al.*, 1977), but it appears that the more a subject is required to perform while intoxicated with cannabis, the greater the rate of tolerance development, as is the case with alcohol and probably other drugs.

Some of these predictions may offer partial explanations for the number of studies (usually toxicological surveys) in which animals were treated with what appeared to be adequate tolerance-inducing doses of cannabis for up to a year (Sullivan and Willard, 1978) without acquiring marked tolerance to behavioral effects. In such studies, perhaps the reason for the small degree of tolerance development is the relatively little behavior required of the caged animal. This may account also for some of the differences in the human tolerance studies with hospitalized volunteers.

Tolerance: Mechanisms

Two general classes of mechanisms are possible. Tolerance results from changes in the pharmacokinetics (i.e., the absorption, distribution or metabolism of THC) or from adaptations at the site or sites of drug action (functional tolerance). This is a crude classification and not nearly as imaginative as that used by some investigators who prefer to break functional tolerance into a variety of subclasses. Some combination of the two main classes of mechanisms is, of course, possible. Although some investigators still occasionally cite learning as a "mechanism" for tolerance, I prefer to maintain the faith that learning and behavior some day will be understood at the cellular and neurochemical level. Thus I have discussed learned or behavioral tolerance in the section on behavioral science rather than describing it as a separate mechanism.

Pharmacokinetic Mechanisms

Although pharmacokinetic changes are rarely the main explanation for tolerance to any psychoactive drugs, they continue to be sought as simpler explanations for tolerance. The search has, not surprisingly, remained unrewarding. It appears that most of the loss of sensitivity to almost all cannabis effects observed in most species cannot be accounted for by pharmacokinetic and metabolic changes (Worm *et al.*, 1971; McMillan and Dewey, 1972; Siemens and Kalant, 1974; Hunt and Jones, 1980). The early finding that radiolabeled THC disappeared about twice as fast in experienced smokers of marihuana as in nonusers (Lemberger *et al.*, 1971a and b) suggested some induction of metabolism. Support for this hypothesis came from other experiments. Magour *et al.* (1976, 1977) suggested that changes in the metabolite levels in rat brains rather than an increase in THC elimination may be responsible for tolerance. Pretreatment of rats with SKF-525A, a microsomal enzyme inhibitor, enhanced THC impairment on behavioral tasks while treatment with phenobarbital, a microsomal enzyme inducer, accelerated the development of tolerance (Davis and Borgen, 1975). Hepatic microsomal activity increased during four weeks of THC treatment (Ho *et al.*, 1973).

Thus, it appears that conditions increasing the metabolism of THC promote tolerance. However, no shift in THC or metabolite levels is seen in the blood or brain of tolerant compared with nontolerant pigeons (Dewey *et al.*, 1973; McMillan *et al.*, 1973) or in dogs (Martin *et al.*, 1976) or mice (Lawrence and Pertwee, 1973; Dewey *et al.*, 1976b). Furthermore, repeated i.p. administration of THC to rats did not stimulate hepatic metabolism of THC (Siemens and Kalant, 1974). Recent studies in mice (Ohlsson *et al.*, 1980) conclude that structural aspects of many monooxygenated metabolites are more important determinants of psychoactivity than their ability to enter the brain, so that differential entry into the brain seems less important a consideration. Differences in the behavioral activity of THC, cannabidiol (CBD) and cannabinol (CBN) also cannot be explained by differential ability to enter the brain or because of differing regional distribution (Alozie *et al.*, 1980).

Related to the metabolic hypothesis of tolerance is the notion that THC activity is due primarily or in part to 11-OH-THC or other metabolites (Lemberger and Rubin, 1976). According to this hypothesis, an increase in metabolic clearance could reduce levels of active metabolites if subsequent metabolism of the active metabolite utilizes the induced enzyme. With 19 subjects given frequent 10 to 30 mg doses of oral THC, no evidence of hepatic enzyme induction was found (Benowitz and Jones, 1977b). Instead, through a combination of increased distribution volume, diminished metabolic clearance and delayed absorption, disappearance of antipyrine, alcohol, and pentobarbital was slowed. Garrett and Hunt (1977) and Hunt and Jones (1980) speculate, on the basis of pharmacokinetic properties of THC in dogs and in humans, that enzyme induction should not dramatically alter the time course of THC concentration in tissues and that increased metabolic activity is most unlikely to be a primary mechanism of tolerance.

Hunt and Jones (1980) compared the kinetics and pharmacological effects of THC in six subjects before and after a period of 10 to 12 days of administration of 30 mg oral THC every four hours. In order to compare THC pharmacokinetics independent of the cannabinoid levels resulting from chronic THC administration, the disposition of 2 mg doses of radiolabeled THC before and after tolerance development was compared. The time course of THC in plasma before and after tolerance development was not dramatically different. The terminal half-life for THC was 19.6 hr before tolerance and 18.7 hr after. The minimal changes in other THC pharmacokinetics seemed insufficient to account for the degree of tolerance that developed to the cardiovascular and subjective pharmacological effects.

CBD is a well established inhibitor of a number of hepatic drug biotransformation reactions (Karler *et al.*, 1974). Chronic CBD administration was far more active in inhibiting a variety of hepatic drug metabolizing systems *in vitro* than was CBN or THC (Fernandes *et al.*, 1973), although tolerance developed in other studies (Borys *et al.*, 1979). Because cannabis contains varying proportions of THC and CBD, it is possible that the CBD content of cannabis could alter effects of repeated cannabis administrations. However, pretreatment with 1,500 mg CBD given as divided doses during the 12 hr prior to i.v. administration of 2 mg radiolabeled THC had no effect on THC pharmacokinetics and only very slightly decreased the extent and rate of formation and excretion of metabolites (Hunt *et al.*, 1981). In other studies in our laboratory we found CBD to be a potent inhibitor of barbiturate metabolism, but it appears to be without other significant biological effects in normal humans (Benowitz *et al.*, 1980).

Functional Tolerance

It is unfortunate that simple metabolic explanations for cannabis tolerance do not seem likely. Mechanisms underlying functional tolerance are more complicated, and difficult to study. Presumably, the mechanisms of functional tolerance (or behavioral, learned tolerance, etc.) have to do with changes in the physical chemistry of cell membranes, altered intracellular mechanisms, or changes in neurochemistry (e.g., alterations in enkephalinergic/endorphinergic systems or other neurotransmitters and neuromodulators that are important in maintaining the integrity of physiological functions, mood, learning, and behavior in general). These are complicated systems. A case can be made that many cannabinoids act by eliciting effects on cell membranes as a result of their high lipid solubility. On the other hand, Mechoulam and Carlini

(1978) think that cannabinoids may act on specific receptors, partially because of the high degree of stereospecificity required to produce an effect (the unnatural (+)-isomer of THC is almost devoid of activity). Both mechanisms may be important, but as a consequence or as a correlate, profound changes in brain biogenic amines, steroids and other biochemical systems occur during tolerance development and presumably during development of dependence (Colombini *et al.*, 1974; Harris *et al.*, 1977; Taylor and Fennessy, 1978a; Miczek and Dixit, 1980).

Tolerance: Reverse Tolerance

Reverse tolerance, an imprecise term, was mentioned in an early, poorly designed study of marihuana effects (Weil *et al.*, 1968), and promptly caught the imagination of scientists and the public (Fox, 1973). Evidence of sensitization in a pharmacological, metabolic, or physiological sense has never since been reported. Numerous investigators state that experienced marihuana smokers report greater levels of intoxication after smoking low doses of marihuana than do less experienced or naive users (Jones, 1971, 1975; Cappell and Pliner, 1974; Carlin *et al.*, 1974; Wikler, 1976). Very early in our studies we reported that whereas very frequent users described more intense subjective effects of a low dose of smoked marihuana, they described less intense effects from oral doses than relatively infrequent marihuana users did. The simplest explanation for this is that the well practiced smoker, besides having better smoking technique, is more influenced by familiar cues associated with smoking and by conditioning influences, which should facilitate the occurrence and perception of previously experienced effects. With oral THC, which was for these users an unfamiliar and unpracticed way of becoming intoxicated, there seems to be, if anything, traditional tolerance rather than facilitation.

Other studies revealed no significant differences in responsiveness between experienced and naive users (Casswell and Marks, 1973; Cohen and Rickles, 1974; Perez-Reyes *et al.*, 1974; Milstein *et al.*, 1975a and b) or found all subjects to show either equal sensitivity or apparent tolerance.

On the basis of one of the earlier metabolic studies, Lemberger *et al.* (1971a and b) and Lemberger and Rubin (1975, 1976, 1978) speculated that because marihuana users have more rapid decline in plasma radioactivity and increased formation of the active 11-OH metabolite of THC, it is plausible that reverse tolerance could be a consequence of enzyme induction which converted THC more rapidly to the more active and presumably more stable metabolite. Recent and better controlled studies suggest that this may not be likely to occur and, given the dispositional characteristics of the cannabinoids, is not likely to explain differences in cannabis effects if it does occur (Hunt and Jones, 1980).

In summary, it probably would be best if the term "reverse tolerance" joined the terms "amotivational syndrome" and "addiction" in well deserved retirement.

Tolerance: Instances When It Does Not Develop

Tolerance to cannabis has been demonstrated so regularly that it is of interest to consider some of the studies in which it did not occur. When a phenomenon does not occur there are usually many alternative explanations, particularly in drug studies (Kaymakçalan and Sivil, 1974; Lewis *et al.*, 1974). By using too low or too infrequent a dose, by not properly considering bioavailability, or by using insensitive, unreliable, or even inappropriate measures of drug effect, it would be easy to demonstrate the absence of tolerance or, for that matter, dependence. However, in a number of published studies in which tolerance was not reported, doses and measures were used that have been associated elsewhere with the development of tolerance. A few examples of such puzzling studies, from both the human and animal literature, follow.

Volunteers with a history of moderate marihuana use smoked an average of three cigarettes per day over 21 consecutive days yet showed no decrease in subjective ratings of intoxication or tolerance to increased heart rate (Babor *et al.*, 1975). Since this study replicated an earlier one by the same group, it is for them a consistent finding (Mendelson *et al.*, 1974a), and important since they interpret the results to mean that tolerance alone is not sufficient to account for the gradual increase in marihuana consumption by these subjects. Other groups studying inpatient and outpatient subjects smoking repeated doses reported a similar lack of tolerance to cardiovascular effects (Frank *et al.*, 1973, 1976; Renault *et al.*, 1974; Rickles *et al.* 1978), despite the many other studies reviewed in this paper that consistently revealed tolerance at the same or lower dose level. Lack of adequate control over dose administration, and insensitive or unreliable measures of drug effect, might explain the failure of these groups to observe tolerance.

In a number of studies in which the effect of a given dose of THC or cannabis was compared in groups of drug-experienced and inexperienced outpatient volunteers, similar problems stemming from lack of adequate control of dose, inappropriate timing of testing after last exposure to cannabis, or relatively insensitive measures of drug effects could have accounted for the absence of any apparent tolerance (Casswell and

Marks, 1973; Milstein *et al.*, 1974, 1975a and b; Perez-Reyes *et al.*, 1974, 1976).

In some instances the claimed absence of tolerance seems to be more simply an alternate interpretation of the data. For example, Pirch *et al.* (1972b) said that, although tolerance developed to many effects of 20 to 40 mg/kg THC given daily to rats, it did not develop to EEG effects. Spindle-like EEG activity increased after three to five days treatment and remained during the 35-day period of drug administration. An alternative explanation would be that the spindle-like activity was the compensatory synchronization that accounted for the observed tolerance to the initial THC-induced desynchronization of the EEG. In other than the unlikely situation where metabolic factors account entirely for tolerance, there must be adaptive mechanisms that produce what we refer to as functional (or pharmacodynamic, etc.) tolerance. If we, as investigators, are fortunate enough to be able to measure correlates of the adaptive mechanisms, or measure these mechanisms directly, then we should not expect to find "tolerance" to those particular processes, except as a consequence of further changes (possibly manifestations of toxicity) resulting from prolonged administration.

Tolerance: Cross-Tolerance

The characteristics of cross-tolerance between cannabis and other drugs might help us to understand their mechanisms of action. Cross-tolerance has clinical significance because of the propensity of people to use drug mixtures. THC in humans has effects at high doses that resemble those of hallucinogens such as lysergic acid diethylamide (LSD) (Jones, 1973), but also effects resembling those of alcohol and other sedative hypnotics (Jones and Stone, 1970). In animals, THC has many pharmacological similarities to morphine and other opiates (Kaymakçalan, 1979).

No cross-tolerance to LSD was seen in humans (Isbell and Jasinski, 1969) or between LSD and mescaline in rats (Silva *et al.*, 1968). Rats tolerant to the effects of THC show asymmetrical and occasionally symmetrical cross-tolerance to ethanol on both behavioral and physiological indices (Newman *et al.*, 1972, 1974; Siemens and Doyle, 1979). Some evidence for cross-tolerance between THC and ethanol was seen in humans (Jones and Stone, 1970; MacAvoy and Marks, 1975). The mechanisms for THC and ethanol cross-tolerance do not seem to be metabolic (i.e., dispositional) interactions (Sprague and Craigmill, 1976; Siemens and Doyle, 1979). That the cross-tolerance between cannabinoids and a number of drugs including alcohol and other sedative hypnotics is not entirely reciprocal suggests shared but not identical functional mechanisms.

Cross-tolerance with stimulant drugs has not been reported. Pigeons tolerant to THC were cross-tolerant to pentobarbital but not to amphetamine or morphine (McMillan *et al.*, 1980). Cross-tolerance with amphetamine was also not observed by others (Hattendorf *et al.*, 1977). Chronic THC injections diminish hexobarbital effects in mice (Sofia and Barry, 1973). McMillan *et al.* (1980) did not investigate pigeons tolerant to pentobarbital to see if symmetrical cross-tolerance was apparent, but they thought that part of the cross-tolerance was due to lower pentobarbital plasma levels in the THC-tolerant pigeons. Such a metabolic mechanism would be consistent with our observations that there was more rapid barbiturate metabolism in THC-tolerant humans (Benowitz *et al.*, 1980).

Because of the marked inhibition of liver microsomal drug metabolizing systems by CBD (Fernandes *et al.*, 1973; Karler *et al.*, 1974; Siemens *et al.*, 1974; Ingall *et al.*, 1978), one might expect some degree of cross-tolerance with drugs that share liver microsomal enzyme metabolic mechanisms. We found that individuals treated for 5 to 12 days with CBD demonstrated markedly inhibited hexobarbital metabolism as compared with pretreatment rates (Benowitz *et al.*, 1980). However, inhibitors of hepatic microsomal drug metabolizing enzymes often act as inducers of these enzymes when given chronically. Indeed, tolerance to this CBD effect may develop under some conditions (Borys *et al.*, 1979). Therefore the finding of cross-tolerance may depend on duration of exposure, and on the amount of CBD present in the liver at the time the other drug is being metabolized.

Thus, interactions between cannabis and other drugs should be expected. The nature of the interaction is going to be complex since, besides possible inhibition or induction of other drug metabolism by THC or CBD, there might also be enzyme induction by constituents in cannabis smoke other than the cannabinoids.

Animal data demonstrating a similar marked but not completely reciprocal cross-tolerance between cannabis or THC and opiates are reviewed in Section 4. Since administration of cannabinoids will not completely suppress the symptoms of the ethanol and the opiate abstinence states, common mechanisms of action are unlikely. It is reasonable to assume that the autonomic nervous system and mood-altering effects of THC partially modify expression of the symptoms of withdrawal from other drugs (i.e., cannabinoids would more probably act at the level of the effector mechanisms than at the opiate receptor or at the site(s) of action of ethanol, wherever it (they) may be). However, as more evidence accumulates about THC-opiate interactions (reviewed in Section 4), it is best to keep an open mind about mechanisms of interaction.

3. SOME GENERAL PRINCIPLES GOVERNING TOLERANCE AND DEPENDENCE

Some of the inconsistencies in the studies with smoked cannabis might be partially understandable if we consider what is known about tolerance and dependence with other drugs. In general reviews of the determinants of tolerance and dependence, a simple but important point is always made, that is often overlooked or forgotten in discussions of cannabis tolerance and dependence. It is that optimal development of both tolerance and dependence is favored by "continued neuronal exposure" to a drug without interruption or with at least sustained periods of exposure (Seevers and Deneau, 1963; Kalant *et al.*, 1971; Goldstein *et al.*, 1974). Failure to recognize this requirement has led to "erroneous conclusions from poorly designed experiments" (Seevers and Deneau, 1963). Seevers and Deneau were discussing opiates, but the same might be said about cannabis studies.

Optimal Conditions for Dependence

It is generally accepted that with a variety of sedative hypnotic drugs and opiates, continued "around-the-clock" chronic administration and intoxication are necessary to demonstrate abstinence phenomena most clearly and quickly (Isbell *et al.*, 1950, 1955; Seevers and Deneau, 1963; Kalant *et al.*, 1971; Goldstein *et al.*, 1974). The popularity and the utility of the opiate slow release delivery systems in animal studies are the best illustration of this. With opiates or alcohol, ordinary conditions of clinical or illicit administration are inadequate to produce maximal dependence rapidly. It is often forgotten that a standard stabilization dose for morphine in the Lexington studies of opiate dependence was in the range of 200 to 400 mg per day given in four equal and spaced doses. This dose is rather large by present day standards of illicit opiate use, but in the Lexington studies it generally yielded only a midgrade intensity of physical dependence (Goldstein *et al.*, 1974).

With opiates, other psychoactive substances and perhaps all drugs, there appears to be a "safe" interdose interval at which tolerance and dependence develop either slowly or not at all. This interval may vary from hours to days depending on the drug's disposition and kinetics (Kalant *et al.*, 1971; Goldstein *et al.*, 1974; Sellers, 1978). With any psychoactive drug, there appears to be a dose level below which measurable physical dependence does not develop even after prolonged and repeated administration, and tolerance, if evident, is minimal. On the other hand, there appears to be no psychoactive drug that has been experimentally tested in what Seevers and Deneau (1963) would term an "adequate experiment" that does not give rise to tolerance, and most produce dependence.

Problems Inherent in Smoking Studies

If some of these general principles are kept in mind when the experiments with cannabis smoking are considered, it should be obvious that perhaps the safe interval was not exceeded when subjects self-selected their cigarettes or, at best, optimal conditions for tolerance and dependence were not met. In any of the chronic smoking experiments it was an exceedingly rare subject who got up during the night to smoke; thus, a 6- to 8-hr drug-free interval was the minimum. We now know that THC is cleared from blood and is metabolized rapidly (Hunt and Jones, 1980; Ohlsson *et al.*, 1980). Therefore, in most of the experiments with smoked marihuana, plasma levels of THC probably were below the threshold level for most pharmacological effects during substantial periods of time. There is, of course, always the possibility of active metabolites, some of which may be cleared more slowly than THC, but the levels of the more slowly cleared metabolites did not appear to be correlated with most cannabis effects by which tolerance is measured and by which dependence might be most obvious. In other words, the time course of observed events seems to follow more closely the blood levels of THC or its most rapidly formed and cleared metabolites (Jones and Hunt, 1980; Ohlsson *et al.*, 1980).

4. DEPENDENCE

Animal Studies

If, as I speculated earlier, tolerance and dependence to so many drugs so often appear and disappear together that they may be "reflections of the same underlying biologic change" (Goldstein *et al.*, 1974), one might properly expect more evidence of dependence from animal studies since profound tolerance is so easily demonstrated. When a phenomenon is not found, there are unfortunately many explanations. In the case of cannabis withdrawal symptoms in animals (assuming they can occur), it may be that species differences, route of administration, dose frequency, and differing kinetics in differing species can make for a situation in which it is much harder to demonstrate dependence than tolerance. This happens with other classes of drugs, such as sedatives (including alcohol), stimulants, nicotine and, to some extent, even opiates. Rarely have animal experiments been done in which optimal conditions for the development of cannabis dependence have been deliberately arranged. When optimal conditions are approached, dependence is usually observed.

Studies reporting naloxone-precipitated abstinence after chronic treatment with THC, THC-related modifications of naloxone-induced withdrawal from morphine, and cross-tolerance between morphine and THC suggest that, at some level, interactions between naloxone or opiate agonists and THC occur. I will review these studies in more detail later. They do not in themselves demonstrate cannabis dependence but, by inference, make the possibility more plausible.

Monkey

In an important study that unfortunately no one has tried to replicate properly, tolerance and physical dependence with an opiate-like withdrawal syndrome were reported to occur in monkeys (Deneau and Kaymakçalan, 1971; Kaymakçalan, 1973). The monkeys received automatic i.v. injections of THC every six hours at gradually increasing doses to a maximum of 0.4 mg/kg. Tolerance developed to the effects observed initially (ptosis, blank staring, scratching, and unusual docility). The monkeys were maintained on the highest dose for 12 days. At the end of the 36-day period of THC administration, when the injections of THC were terminated abruptly, abstinence signs appeared about 12 hr postdrug and continued for about five days. These included yawning, anorexia, piloerection, hyperirritability, increased aggressiveness, scratching, finger biting and licking, hair pulling, tremors, twitches, penile erection and masturbation with ejaculation, and eating of feces. Hallucinations were suggested by such behaviors as staring in circles, slapping cage walls, and grasping as if trying to catch nonexistent flies.

Before the chronic THC administration, none of the six monkeys would self-administer THC, but during the abstinence phase two did initiate and continue i.v. self-injection. The three who did not self-inject were allowed to self-inject cocaine. Two of those three did not self-inject cocaine (which perhaps is worthy of note), but the third one initiated and maintained cocaine self-administration. When cocaine was replaced by THC (0.4 mg/kg) this animal continued to self-administer THC. The three monkeys that self-administered THC were allowed to continue doing so for 3 to 8 wk more. The self-administration rate varied between 5 and 30 times daily, mostly during daytime hours. Abrupt cessation of drug was followed by characteristic withdrawal symptoms. During the withdrawal phase the three animals repeatedly pushed the button controlling self-administration.

A number of other investigators have chronically treated monkeys with similar doses of THC or synthetic analogs, but generally for shorter periods of time that resulted in milder withdrawal signs (Fredericks and Benowitz, 1980). Even more importantly, they have employed once- or twice-a-day dosage schedules, rather than the every-six-hour automatic dose schedule (Deneau and Kaymakçalan, 1971; Kaymakçalan, 1974), and have observed no withdrawal signs (Hardman *et al.*, 1971; Ferraro, 1972; Harris *et al.*, 1972; Heath, 1976; Chapman *et al.*, 1979; Heath *et al.*, 1979; Sassenrath *et al.*, 1979).

Stadnicki *et al.* (1974b) described what could be considered withdrawal signs in monkeys following chronic oral administration of a crude marihuana extract for 50 days at a dose of 37.5 mg/kg. Two of the three monkeys showed increased aggressiveness upon withdrawal. One had increased periods of EEG desynchronization and demonstrated behavior that was consistent with the presence of hallucinations.

Monkeys given a lower dose (0.5 mg/kg every 6 hr for 3 wk) showed increased gross movement, eye contact, and tooth baring when the THC was suddenly discontinued. Only those behaviors that were initially suppressed by the THC and to which tolerance developed showed what appeared to be a rebound phenomenon in the week post-THC (Fredericks and Benowitz, 1980).

Rat and Mouse

Spontaneous withdrawal signs after chronic THC treatment in rats have not been described as dramatically as they have been in monkeys. Rats given s.c. injections of 25 mg/kg THC for 20 days demonstrated, on the second withdrawal day, motor activity that was increased over baseline levels. No attempt was made to reverse this by the re-administration of THC (Davis *et al.*, 1972). After a two-week diet of cannabis leaf, mice appeared more aggressive one week after withdrawal (Cutler *et al.*, 1975) but controls were questionable. What appears to be increased aggression is not uncommon in rats chronically treated with cannabis (Abel, 1975). In a study of open-field behavior, rats given a daily dose of 2.5 mg/kg THC for two weeks showed a transient increase in rate of grooming when THC administration was stopped (Sjöden *et al.*, 1973). The rat electrocorticogram showed tolerance with decreased amplitude after 5 to 12 days treatment of oral THC and then a rebound of EEG amplitude above baseline values upon withdrawal (Pirch *et al.* 1972a and b, 1973). No attempts were made to reverse what might have represented a withdrawal rebound by giving more THC.

Rats given THC at a fixed dose level of 10 mg/kg for up to 140 consecutive days showed hypersensitivity and hyperreactivity, increased aggression, tremors, and what appeared to be clonic convulsions after two or three months of chronic treatment (Stadnicki *et al.*, 1974a). Although no clear abstinence syndrome was noted on withdrawal, the EEG and behavioral changes are consistent with the development of physical dependence during the fixed dose schedule. Such a phenomenon would not be surprising if one did the same experiment with alcohol. Mice treated with oral doses of THC from 10 to 80 mg/kg for 28 consecutive days showed no withdrawal effects when treatment was stopped and did not have a change in i.v. pentylenetetrazol convulsion thresholds (Chesher and Jackson, 1974). In contrast, mice treated in a similar way with ethanol showed reduced convulsion thresholds, which was interpreted as evidence of dependence. Thus, these oral doses of THC seem to be less potent for inducing dependence by these criteria than the parenteral treatment. THC seems to either suppress or stimulate brain excitability depending on treatment duration (Karler and Turkanis, 1975; Feeney, 1979).

In one study with rats (Corcoran *et al.*, 1978), the main goal was to look at the anticonvulsant effects of THC on seizures precipitated by amygdaloid stimulation. Not only did marked tolerance to the antiseizure effects of THC develop very rapidly, but a dramatic and unanticipated increase in seizure duration occurred on nontreatment days when the rats had been receiving 45 mg/kg (i.p.) of THC every other day for six days. The authors thought the phenomenon reflected physical dependence and emphasized that it occurred only at the very high and toxic dose. One mg/kg THC over the same interval did not produce such an effect. Others have reported either a similar increase of CNS excitability after two or three days treatment with anticonvulsant doses of THC (Karler and Turkanis, 1975, 1976, 1980), or phenomena that could be explained by increased CNS excitability (Haïlé *et al.*, 1975). However, in studies where similar doses and schedules have been employed, postdrug hyperexcitability does not always occur (Leite and Carlini, 1974).

THC and Naloxone Interactions

The narcotic antagonist, naloxone, given to rats treated chronically with THC, precipitates a set of behaviors with many characteristics of opiate withdrawal (Hirschhorn and Rosecrans, 1974; Kaymakçalan *et al.*, 1977; Tulunay *et al.*, 1980). Ten rats were treated twice daily for five weeks with THC s.c. in doses that increased gradually to a maximum of 40 mg/kg for the last three weeks (Kaymakçalan *et al.*, 1977). This high dose produced marked tolerance to the hypothermic and behavioral effects. Administration of an i.p. single dose of 1.0 or 4.0 mg/kg naloxone on the 22nd and 31st days abruptly precipitated an opiate-like abstinence syndrome. Termination of THC treatment on the 35th day also produced a similar syndrome that peaked 48 hr postdrug. Common signs of abstinence included teeth chattering, defecation, urination, difficulty in breathing, and closed eyes. More inconsistent behaviors included chewing, head tremor, jumping, escape behavior, and biting of fingers. Locomotor activity increased. Hirschhorn and Rosecrans (1974) described similar naloxone-precipitated phenomena in THC-tolerant rats.

Recently, Tulunay *et al.* (1980) demonstrated that naloxone (1.25 to 20 mg/kg) precipitated opiate-like withdrawal signs in rats after only five injections of THC over a three-day period. As with opiates, the intensity of the naloxone-precipitated THC abstinence syndrome was dependent on the doses of both THC and naloxone. Abstinence scores in the THC-exposed rats challenged with naloxone did not differ from those in placebo-treated animals when the dose of THC was less than 10 mg/kg. However, they increased in a dose-dependent fashion in the groups treated with 10 to 40 mg/kg THC. Piloerection, teeth chattering, chewing, abnormal posture, and jumping were most prominent at the 20 and 40 mg/kg THC doses.

In a recent study, chlornaltrexamine, a selective irreversible opiate antagonist which cannot be displaced from its receptor site, inhibited THC-induced analgesia, hypothermia, tolerance to the hypothermia effect, and physical dependence development. This provides further evidence that THC may produce some (but not all) of its pharmacological effects through opioid-related mechanisms (Tulunay *et al.*, 1981). In this study, THC-treated rats (20 mg/kg for three days) showed more intense naloxone-precipitated withdrawal on the fourth day (after 5 mg/kg naloxone) than did the animals treated with both THC and chlornaltrexamine.

Other THC/Opiate Similarities

The similarities between opiate- and naloxone-induced and spontaneous THC abstinence are consistent with other features that are common to cannabis and the opiates. Given the diverse opiate/naloxone/THC interactions that might occur via some mediation by the enkephalin/endorphin or other neurotransmitter/neuromodulator systems, a variety of relationships is possible. Morphine and THC share a number of pharmacological effects (Bloom and Dewey, 1978), including antinociceptive activity, increase in catecholamine synthesis, and hypothermia (Kaymakçalan, 1975, 1979). Naloxone blocks these effects of THC metabolites and related substances, just as it does with opiates (Wilson and May, 1975; Bloom *et al.*, 1976, 1977). The mixed narcotic antagonist-agonist nalorphine does not antagonize THC action (Chesher *et al.*, 1973). An asymmetrical cross-tolerance between THC and morphine occurs, with morphine-tolerant animals also showing tolerance to the antinociceptive effects of THC. Animals tolerant to the hypothermic effects of THC are tolerant to the hypothermic action of morphine (Bloom and Dewey, 1978). In one of the earlier studies, McMillan *et al.* (1971) reported that chronic THC treatment decreased the effects of morphine on the mouse tail-flick test; this result also suggested cross-tolerance. This pattern of findings, together with reports that THC decreases the severity of naloxone-induced withdrawal from morphine (Hine *et al.*, 1975; Bhargava, 1976, 1978), suggests that THC may be active at naloxone-sensitive sites of opioid action. On the other hand, THC potentiated the action of morphine on motor activity in mice. Tolerance developed to the potentiating action of THC on morphine-induced hyperactivity as tolerance developed to the morphine. Cross-tolerance between the locomotor effects of morphine and THC has also been reported (Ayhan *et al.*, 1979), but a very old study with morphine-tolerant dogs reported no cross-tolerance to cannabis extract (Myers, 1916).

THC has a potency similar to that of morphine in suppressing the quasi-morphine withdrawal syndrome, but unlike the effects of morphine those of THC were not reversed by naloxone (Zaluzny *et al.*, 1979). The mechanism here is unclear.

The data reviewed above are compatible with the possibility that naloxone may interact with the cannabinoids at different sites from those at which it interacts with the opiates. Dewey *et al.* (1976c) have speculated that some of the inhibitory effects of naloxone on THC-increased catecholamine synthesis are intraneuronal. It is unlikely that interactions between cannabinoids and narcotic analgesics occur on the same receptors because of the differences in chemical structure. Although little has been written about THC-receptor interactions, the pattern of effects of THC on the uptake of biogenic amines and on behavior may be due to receptor-blocking effects, with consequent THC-increased uptake of DA, NE, 5-HT and GABA (Hershkowitz and Szechtman, 1979). Perhaps the THC also alters affinity of opiates to opiate receptors. As an alternative and plausible explanation, THC, morphine, and naloxone may interact at the level of brain neurotransmitters independently of any interaction at the binding site or receptors (Ülkü *et al.*, 1980).

Other Possible THC Antagonists

Because the tricyclic antidepressant clomipramine antagonizes the body temperature changes induced by THC and the decrease in 5-OH-indoleacetic acid (Taylor and Fennessy, 1978b; Fennessy and Taylor, 1979), its ability to precipitate a withdrawal reaction in THC-tolerant rats was investigated. Rats given 2 to 6 mg THC twice daily i.v. for 10 days were given clomipramine (15 mg/kg). Over the next 30 min the THC-treated rats showed writhing, wet shakes, jumping, and backward kicking of hind legs. This was interpreted as representing a state of physical dependence unmasked by a THC antagonist. The authors speculated that clomipramine may act as an antagonist by interfering with the uptake of 5-HT into tryptaminergic neurons. This is plausible in that THC seems to exert at least some of its action through serotonergic pathways (Sofia *et al.*, 1977). For example, following pretreatment with 5-HT-depleting drugs or after 5-HT pretreatment the effects of acute marihuana treatments are altered (Adams and Barratt, 1975b). However, certainly other neurotransmitters and neuromodulators are involved in the actions of marihuana (Singh *et al.*, 1978; Miczek and Dixit, 1980) so that the specificity and the mechanisms of this so-called antagonist will need further investigation.

Studies of other effects of cannabis on brain neurotransmitter systems have produced widely varying results (Harris *et al.*, 1977). Data have recently been presented suggesting that THC increases synthesis of 5-HT by altering, by some unknown mechanism, the quantity of tryptophan available for conversion to 5-HT (Johnson and Dewey, 1978). The effects of clomipramine might be to increase suddenly the concentration of 5-HT in the vicinity of neurons and, if 5-HT release has been chronically decreased during prolonged THC treatment, one might expect a postsynaptic supersensitivity.

Dependence: Human Studies—Smoked Cannabis

Both the existence and characteristics of cannabis dependence are far more controversial an issue than tolerance now is. The average North American cannabis user would argue even more vehemently than the scientists that they have not observed withdrawal symptoms after cessation of cannabis use. Of course, most users still argue that tolerance does not develop. A few users might admit to "psychological dependence" (Mirin *et al.*, 1971; Weller and Halikas, 1980). Similar arguments pro and con about alcohol and barbiturate tolerance and dependence were discussed and published earlier in this century. As we shall see, this attitude among users may be changing slightly.

Clinical Reports of Dependence

Uncontrolled clinical observations suggesting withdrawal syndromes in patients are appropriately suspect. One early report described insomnia and asthenia in chronic users of cannabis when they stopped taking the drug (Bard, 1941). Chronic use was described as being comparable to alcoholism. Fraser (1949) described hyperirritability, frightening auditory and visual hallucinations, and incessant masturbation lasting for three to five weeks in a small group of Indian ganja smokers who were unexpectedly deprived of cannabis. Three young students who had been smoking an unknown amount of pure hashish daily were observed to have increased sweating, disturbed sleep, tremor, muscle weakness, and depressed mood when deprived of hashish (Kielholz and Ladewig, 1970). Egyptian hashish smokers were described as experiencing dysphoria, irritability, negativism, and insomnia when the drug was no longer available (Soueif, 1967). A similar pattern was described in five South African cannabis smokers who experienced anxiety, restlessness, abdominal cramps, nausea, increased heart rate, and sweating when cannabis unexpectedly was not available (Bensusan, 1971). Indian users of 40 to 350 mg THC daily were described as showing rapid tolerance to dose increments and abstinence symptoms (irritability, yawning, anorexia, tremors, cramps, insomnia, and photophobia) beginning a few hours after the last dose and lasting three to four days (Chopra and Jandu, 1976). Symptoms were lessened by the administration of alcohol or barbiturates. An earlier Indian monograph also made mention of mild withdrawal signs in both humans and rats (Chopra and Chopra, 1939). However, another report by one of the same authors said withdrawal effects were almost nil (Chopra, 1935). In a letter to the editor, three cases of manic-depressive illness following prolonged use of marihuana were described. The author wondered if others had similar experience and whether it represented withdrawal behavior (Teitel, 1977).

With such reports one can never be certain about the concurrent use of other drugs such as opiates or alcohol that could confound the clinical picture, or the possibility of coincidental infectious, mental, or physiological disorders that could account for such symptoms and behavior. However, since a similar clinical picture develops under more controlled laboratory circumstances (see below), perhaps we should not completely dismiss these uncontrolled clinical reports.

Semi-Controlled Observations

Under slightly more controlled circumstances, hashish users studied in Greece reported they felt irritable, anxious, and had what was termed unpredictable emotional outbursts when they failed to obtain hashish each day. These symptoms were replaced by a relaxed and drowsy state after the smoking of the drug (Fink, 1977). However, such changes in behavior were not noted in these volunteers during a three-day abstinence period in a clinical laboratory setting (Stefanis *et al.*, 1976b). In a controlled comparison of users and nonusers in Costa Rica, regular cannabis users showed more disturbed sleep and altered sleep EEG patterns when studied after about 10 hr of abstinence from cannabis (Karacan *et al.*, 1976).

Marihuana and Pyrahexyl: In even more controlled circumstances, smoked marihuana and oral pyrahexyl were administered in a research ward setting for 39- and 28-day periods, respectively (Williams *et al.*, 1946). On average, 17 cigarettes were smoked daily (range 1–26) amounting to about 12 to 23 g of what was termed by the smokers "good weed." Most of the marihuana-smoking subjects reported feeling "jittery" after withdrawal, but did not appear so by observation. Caloric intake, plasma volume, and weight decreased in the postmarihuana period. Pyrahexyl is a semisynthetic THC-like drug which has a longer duration of action than THC and is about one-third as potent (Hollister *et al.*, 1968). The amount of pyrahexyl was self-selected and ranged from 60 to 2,400 mg daily administered in a range of 1 to 8 doses. This would be approximately equivalent to a daily dose of 20 to 800 mg oral THC. Sustained intoxication was maintained and tolerance developed (see Section 2: Studies in Controlled Environments). The hospitalized subjects became hyperirritable and dysphoric when the pyrahexyl was stopped. Weight loss, decreased sleep, decreased caloric intake, increased body temperature, and increased pulse rate began to appear two days following the sudden cessation of pyrahexyl administration. On the third withdrawal day, most patients were restless, slept poorly, had poor appetites, and reported hot flashes. There was increased perspiration and two subjects had difficulty swallowing.

One subject in the pyrahexyl study had a history of schizophrenia. He developed trembling on the second day of withdrawal as though he were having a chill. He became agitated, fearful, restless, and slept poorly. This became worse on the third day when he appeared disoriented as to time and place. There were mood swings and chewing of fingernails, crying, and inability to swallow. These symptoms disappeared for a 4–5-hr period after more pyrahexyl was given. They worsened as the effects of the pyrahexyl wore off. He was finally treated with a combination of morphine, pentobarbital, pyrahexyl, and phenobarbital with gradual disappearance of the symptoms over an 8-day period. A second pyrahexyl-treated subject developed what was termed a hypomanic reaction reaching its maximum intensity on the fourth day of withdrawal. There were hyperactivity, euphoria, increased psychomotor activity and inappropriate behavior, all of which were unexpectedly *enhanced* by smoking three marihuana cigarettes. The behavior disappeared completely by the eighth day after withdrawal.

The authors concluded that, although tolerance developed, "the presence of physical dependence was not established." Again, I remind the reader that this study was done with the opiate dependence model in mind. It was published before the experimental alcohol-barbiturate dependence studies referred to earlier (Isbell *et al.*, 1950, 1955). As was the tradition in those days, placebo controls were not used. It is unclear just what the volunteer subjects or investigators expected to happen.

However, subjects were in a controlled environment where persistent use of other drugs during the experimental trials was unlikely. The timing and intensity of the changes during drug withdrawal were only slightly different from those observed in more recent studies (Jones *et al.*, 1981). The clinical picture is consistent with the uncontrolled clinical observations referred to in Section 3: Optimal Conditions for Dependence. The longer acting oral drug pyrahexyl appeared to produce a more marked dependence than the shorter acting smoked cannabis.

McLean Hospital/Boston: In a more modern and extensive version of the Williams *et al.* (1946) cannabis smoking studies, Mendelson *et al.* (1974a and b, 1976a, b, c) and Greenberg *et al.* (1976a and b) studied frequent and less frequent marihuana users living on a well-controlled research ward at McLean Hospital in Boston. The volunteers were allowed to smoke self-determined doses of cannabis for a 21-day period. Consumption generally ranged from about three to six one-gram marihuana cigarettes (each containing about 20 mg THC) daily, though one subject smoked up to 20 cigarettes. Although the investigators in these studies did not see anything that they considered evidence of dependence, they reported that some subjects did experience rapid weight loss, decreased appetite, tremor, increased urine specific gravity, and what was described as increased anxiety, hostility, decreased friendliness, and a generally dysphoric mood after the end of three weeks of smoking. The omission of any placebo treatments, the use of a single nonblind dose schedule, and the subject-controlled doses in these studies unfortunately confound and limit the interpretation of these post-smoking changes. Subjects obviously were aware of the treatment schedule and study termination date, so that some of the mood changes might be more related to leaving the hospital and terminating the study than to stopping smoking cannabis. However, the other behavioral and physiological changes observed are less likely to have been determined by such factors.

Canadian: In a study with lower cannabis doses, six subjects smoked cannabis over a 42-day period while hospitalized on a research ward (Miles *et al.*, 1974). Mean consumption ranged from about 10–60 mg THC per day. Although subjects judged the potency of the marihuana to decrease progressively, no clear tolerance was noted. The self-selected dose increased slightly over the period of administration. No abstinence signs or symptoms were noted, but self-determined alcohol consumption rose to the highest level of the entire hospitalization period on the few days following the termination of cannabis smoking. Whether this represented cross-dependence between THC and alcohol or just celebration of the study termination could not be determined because of the study design. No placebo or double-blind dose manipulation was tried.

UCLA: In an equally comprehensive study with much longer cannabis exposure done at the University of California at Los Angeles (UCLA), volunteers lived for 94 days in the hospital (Cohen *et al.*, 1976). They smoked self-determined doses of marihuana cigarettes similar to those used in the Mendelson *et al.* (1974a and b, 1976a, b, c) studies. After an average dose of 5 (range, 1.7–10) cigarettes per day, each containing about 20 mg THC, for a 64-day period, some subjects appeared restless and experienced insomnia, anorexia, mild nausea, and irritability on cessation of smoking. Although daily THC exposure was 34 to 199 mg, *ad lib* smoking was allowed only between 4 p.m. and midnight. One compulsory marihuana cigarette was smoked each morning. Thus most subjects probably had fairly low plasma THC levels for 12 or more hours daily because of the irregular pattern of smoking. For similar reasons but to a lesser degree, the same was probably true of most subjects in the McLean Hospital chronic smoking studies.

At UCLA, as in all the other *ad lib* studies, subjects gradually increased the number of cigarettes smoked per day during the nine-week smoking period. Tolerance developed rapidly to cardiovascular and subjective effects of a standard cigarette smoked in the laboratory each day. The trend was evident the first week and significant by the second week. Tolerance developed faster in the more frequent smokers (Nowlan and Cohen, 1977). Tolerance to respiratory depressant and other respiratory effects developed more slowly (Bellville *et al.*, 1976; Tashkin *et al.*, 1976).

Tolerance was lost rapidly as well. With each successive cigarette during each evening (4 p.m. to midnight), the increase in heart rate became smaller. However, this tolerance was partially lost each night during the cannabis-free period (perhaps about 12 hr). Also, after one week of abstinence there was partial recovery of cardiovascular and subjective effects when smoking was resumed. This pattern is similar to that seen in the heart rate changes in tobacco cigarette smokers, who show partial loss of nicotine tolerance during sleeping hours each day and rapid reacquisition of tolerance each morning when tobacco smoking is resumed.

Similar subjects (N = 36) studied earlier on the same research ward, but smoking only one cannabis cigarette containing 20 mg THC for 28 consecutive days, showed no tolerance and no cumulative effects on an extensive battery of physiological and behavioral measures during drug administration and apparently showed no withdrawal effects at the end of this period (Frank *et al.*, 1973, 1976).

Since in both of the UCLA studies "quantifiable measurements" of likely withdrawal signs and symptoms were not made (Nowlan and Cohen, 1977), the investigators are perhaps appropriately cautious in their interpretation of the behavioral changes that followed the smoking period. The UCLA group speculated that the sleeplessness, anorexia, nausea, and irritability that developed after cessation of smoking reflected both "pharmacological" adjustment and the "monotony of ward life unrelived [sic] by smoking" or represented "physiological and psychological adjustments to a week without smoking after 64 days of daily intoxication." That the more frequent smokers showed more symptoms seems ignored. The phrases quoted suggest the authors are trying to talk themselves out of saying dependence occurred. This is similar to what was said by the McLean Hospital investigators about mood and behavior changes after the smoking period (see discussion below) (Mendelson *et al.*, 1974a).

As in the McLean studies, double-blind or placebo control treatments were not included, making for possible confounding of the effects of study termination and expectations and attitudes of the research staff and subjects with pharmacological factors.

Columbia/New York City: In a study at Columbia University of hospitalized normal volunteers smoking marihuana, that is described only briefly, a similar experimental format was used but a slightly higher dose of marihuana administered (Georgotas and Zeidenberg, 1979). Five volunteers who had prior experience with marihuana smoking lived for 12 wk on a hospital ward. No marihuana was available the first four weeks. Gradually increasing numbers of marihuana cigarettes containing 20 mg THC were then given. The subjects were required to smoke at least 10 cigarettes a day by the 10th day of drug administration. Thereafter, they were allowed to smoke as much as they wished for the remainder of the 4 wk treatment period. Twenty-two cigarettes per day was the maximum consumption. A second four week marihuana-free period followed. During the final two weeks of smoking, subjects were withdrawn and apathetic. They complained that the marihuana seemed less potent than at the beginning of the experiment. During the first week after smoking stopped they became irritable, uncooperative, hostile, and complained of sleep disturbances. These symptoms and behaviors gradually lessened over the final three weeks of the study.

Thus, in all three of these studies with repeated administration of smoked material, similar changes followed cessation of smoking. Larger doses such as in the Georgotas and Zeidenberg (1979) experiments or longer periods of administration of a slightly lower dose, as in the Nowlan and Cohen (1977) study, may have produced more evidence of dependence than did the intermediate dose level used in the McLean Hospital studies.

Some Problems of Interpretation of Data from Cannabis Smoking Studies

Since none of the aforementioned studies was really designed primarily to study issues of tolerance and dependence, only cautious conclusions are appropriate. The absence of double-blind or placebo controls, or of re-administration of drug to see if assumed withdrawal symptoms were alleviated, is a serious limitation. Less than optimal assessment techniques were used to look for abstinence signs and symptoms. That the dose and smoking pattern in the McLean, UCLA, and Columbia studies were subject- rather than experimenter-controlled is a limitation since the subjects followed varying patterns of administration.

Another potential problem in the McLean studies was that some subjects in at least part of the study were able to save small portions of marihuana from the cigarettes they had been smoking with the intent of smoking it during the five-day postmarihuana period at the end of the study. The investigators thought the amounts actually smoked surreptitiously were too minor to affect any of the results of their research, though such uncontrolled drug use might have more of an effect on the appearance of withdrawal symptoms and signs than it would have on other aspects of the study (Mendelson *et al.*, 1974a).

Investigators in the various studies had different interpretations and probably different definitions of what the manifestations of dependence might be. For example, in the McLean studies it was noted that mood ratings obtained during the postmarihuana smoking period were the "obverse" of those reported during the marihuana smoking. To the investigators this suggested a rebound reaction during the postmarihuana period. However, they appropriately speculated that these predominantly "negative" moods during the postmarihuana period may have been related to subjects' concerns about future plans, leaving the hospital, etc. Of more significance conceptually is that they speculated that the "negative" postmarihuana smoking moods were a "compensatory reaction" to the "extended period of repeated marihuana-induced positive mood state patterns." There may be only a semantic difference between a "compensatory reaction" to a prior drug state and a withdrawal reaction due to "denervation supersensitivity" which, in a way, is also a compensatory reaction to an extended drug-induced state. As already mentioned, the UCLA investigators made a similar interpretation. However, in reviewing earlier studies, one finds more than just semantic problems in discussing observations. There are hints that conceptual differences may sometimes lead observers to be more sensitive or less sensitive to seeing signs, symptoms, and behaviors, and also may influence their interpretation of the observations.

Tolerance and Dependence in Humans: Oral Cannabis and THC

Advantages of Oral Doses

Bearing in mind some of the principles that are discussed in Section 3, we designed specific experiments to study cannabis tolerance and dependence under optimal conditions selected for the development of these phenomena. The individual doses were selected to produce levels of intoxication similar to those experienced in the marihuana smoking studies and to be comparable to doses used extensively in a number of laboratories to investigate the acute effects of cannabis or THC (Hollister *et al.*, 1968; Hollister and Tinklenberg, 1973; Linton *et al.*, 1975; Tinklenberg *et al.*, 1976). However, we selected a dosage schedule whereby these reasonable doses were given every three or four hours, day and night, for a period of time. Such a schedule might sound excessive and unrealistic, but if one considers the pharmacokinetics of THC and, more importantly, the time course of the effects induced by a single dose of THC or cannabis, one realizes that a three- or four-hour dose schedule is quite reasonable and necessary to maintain some fairly constant level of intoxication (Hunt and Jones, 1980; Ohlsson *et al.*, 1980).

This study of cannabis dependence was designed to include laboratory conditions similar to those that were previously found necessary to demonstrate tolerance and dependence with opiates and sedative hypnotics (Isbell *et al.*, 1950, 1955; Seevers and Deneau, 1963). Given the factors that produce optimal conditions for development of tolerance and dependence to almost any psychoactive drug, one should not be surprised that both tolerance and dependence developed after only short periods of cannabis or THC administration in this study.

Methods

These studies, done over about six years and involving 120 volunteer subjects, have been described in a series of publications (Benowitz and Jones, 1975, 1977a and b; Benowitz *et al.*, 1976, 1980; Jones and Benowitz, 1976; Jones *et al.*, 1976, 1981). What follows is a summary overview.

The volunteers lived on a hospital research ward for two to six weeks. All were male, and well experienced in the use of marihuana. The precise sequence of treatments varied slightly from substudy to substudy. Generally, a three- to seven-day placebo treatment period followed admission. Then, under double-blind conditions, oral 10 to 30 mg doses of either pure THC or THC in cannabis extract were given every three or four hours for a continuous 5-to-21-day period. Fifteen subjects received only CBD during hospitalization and provided what amounted to a placebo-only comparison group, since it appears that CBD is without apparent behavioral or psychological effects on any measures used (Mincis *et al.*, 1973; Benowitz *et al.*, 1980).

After the 5-to-21-day period of sustained drug administration and gradually decreasing levels of intoxication, subjects were abruptly switched back under double-blind conditions to oral placebo medication for four to eight days. With six subjects, cannabinoids were again restarted after this drug-free period to see if whatever physiological or behavioral changes followed THC cessation could be decreased or eliminated. Depending on the purpose of the particular substudy, occasional challenge doses of smoked marihuana or i.v. doses of THC were given to study cross-tolerance and pharmacokinetic and pharmacodynamic changes.

THC doses were selected to produce maximal levels of intoxication consistent with safe ambulatory care. Twelve subjects were given a crude ethanolic extract of cannabis. The extract produced a pattern of effects similar to those of pure THC. Therefore, the rest of the experiments were done with pure THC. The 3-to-4-hr dosage schedule was selected because the time course of most effects suggested the need for frequent doses if a reasonably constant THC blood level or at least a steady level of intoxication was to be maintained. This was a fortunate decision because, as the pharmacokinetics of THC and blood levels became better understood, the 3-to-4-hr dose schedule appeared to be the minimum that was adequate for this purpose (Hunt and Jones, 1980; Ohlsson *et al.*, 1980).

In our studies, peak plasma levels of THC after 30 mg oral doses (in sesame oil) were similar to and generally less than those produced by smoking medium potency cannabis cigarettes (Ohlsson *et al.*, 1980). However, because of the dosage schedule and the selection of the oral route, plasma THC levels remained close to pharmacologically active levels between doses.

Tolerance

Tolerance to many of the subjective drug effects was evident after only a few days of 10 mg doses repeated several times daily. For example, there was a 50% decrease in intoxication level produced by a 30 mg oral dose when it followed even four days exposure to the 10 mg doses. On drug symptom ratings and as judged by nursing staff observations, the intensity of initial drug effects diminished 60% to 80% after about 10 days at the sustained 30 mg doses. This, of course, was a more marked degree of tolerance than was observed in any of the previously described experimental studies with repeated smoked doses. Increasing a single oral dose by 30% to 50% usually produced a prompt and temporary return in symptom intensity, thus meeting one criterion for the full definition of tolerance that has been rarely tested in studies with smoked material. The rate of development of tolerance to the subjective effects of cannabis was virtually identical to that following sustained administration of about 100 mg morphine daily to former opiate addict volunteers in the Lexington hospital studies (Martin and Fraser, 1961). Thus, in humans as well as in animals, the rate at which tolerance develops to some cannabis effects is at least as great as one expects with opiate drugs.

On sustained THC administration, tolerance developed to the EEG effects (Herning *et al.*, 1979). The initially observed heart rate increases, skin temperature decreases, intraocular pressure decreases, and salivary flow decreases gradually disappeared. Partial or complete return to predrug levels was observed after about 10 days of continued administration, and was followed by a rebound above pre-THC levels after sudden cessation. Periodic challenge doses of smoked or i.v. THC given during the course of oral THC administration demonstrated that the tolerance was independent of the route of drug administration. A smoked challenge dose of 20 mg THC produced virtually no cardiovascular and only minimal subjective changes after only a few days of repeated oral administration of 20 or 30 mg THC. Tolerance was acquired more rapidly when 20 mg THC was given every 3 hr than when 30 mg THC was given every 4 hr. This suggests that it is the circulating levels of THC or very rapidly formed and rapidly cleared metabolites that are important pharmacologically, rather than the more slowly produced and slowly cleared metabolites. That is, the changes in the drug effects we measured seem to be more a function of the rapid alpha phase of THC clearance lasting minutes rather than the beta phase which is slower ($t_{1/2} = 18.7 \pm 4.2$ hr) (Hunt and Jones, 1980). A similar correlation was reported by Ohlsson *et al.* (1980).

Mechanism

As with the animal studies, the mechanisms of tolerance in humans appear to be more related to adaptation at the sites of drug action than to changes in drug metabolism. The pattern of diminished peak effects after smoked or i.v. doses of THC in people tolerant to oral THC is more consistent with a functional than a metabolic mechanism. Intravenous ^{14}C-THC was given to six subjects before and at the end of the oral THC administration period. The small increases in clearance of THC and its metabolites could not account for the degree of tolerance that we observed (Hunt and Jones, 1980). This conclusion disagrees slightly with that of Lemberger and Rubin (1978) who found shorter plasma half-lives of THC in chronic marihuana smokers compared with naive subjects. However, all investigators agree that the degree of tolerance to certain effects of THC could not be accounted for by metabolic or dispositional alterations.

Abstinence

An abstinence syndrome reflected by subjective mood and symptom reports, behavioral changes, and physiological changes rapidly appeared when the THC administration was suddenly stopped and oral placebo begun. Some subjective reports and observed symptoms are listed in Table 2 where the percentages of subjects reporting various symptoms before, during, and after THC or CBD administration are compared. The postdrug period refers to the placebo administration period beginning at 8 a.m. on the day after THC was stopped. The final THC dose was usually the 4 p.m. or the 8 p.m. dose. Subjects who complained during interviews of at least one occurrence of the symptom at some time during the period covered were tallied. Thus, the table shows only the frequency of complaints and not the intensity, which varied. Some complained more than others, possibly because of personality differences (Bachman and Jones, 1979). Research staff and nursing staff observations were consistent with the subjects' self-reports.

Changes in behavior on the ward and in the laboratory were coincident with the changes in subjective reports and began 5 or 6 hr after the last THC dose. The most consistent and prominent symptoms and behavioral changes were increased irritability and restlessness in formerly relaxed nonirritable patients. Insomnia, anorexia, increased sweating, and mild nausea were universally reported although these symptoms varied in intensity.

Objective changes included a precipitous drop in body weight over four days. Mean decrease was 3.2 kg, though some subjects lost as much as 5 kg. Weight then stabilized at the pre-THC treatment level. Hand tremor and intraocular pressure increased above pre-THC level, and there was a large decrease in the percentage of time spent in rapid eye movement sleep (Feinberg *et al.*, 1975, 1976). Salivary flow and body temperature increased. Both the objective and subjective withdrawal phenomena were diminished for 2 to 3 hr by smoking a marihuana cigarette containing 20 mg THC or by restarting the oral THC administration under double-blind conditions. Smoking a placebo marihuana cigarette did not give relief. Many subjective symptoms were partially relieved by modest doses of alcohol or hexobarbital. The peak intensity of most signs and symptoms was greatest about 8 to 12 hr after stopping THC, though the time varied from symptom to symptom. Most were diminished by 24 hr after cessation and were not measurable after three

TABLE 2

Symptoms During Phases of Drug Administration

	Predrug (%)		Early Drug (%)		Late Drug (%)		Postdrug (%)	
	THC	CBD	THC	CBD	THC	CBD	THC	CBD
Disturbed sleep	28	20	6	6	4	0	89	6
Decreased appetite	6	6	9	13	9	6	81	0
Restlessness	4	6	11	13	6	0	89	13
Irritability	15	13	23	13	9	6	62	6
Sweating	2	6	4	6	6	0	55	6
Chills	4	0	4	0	6	0	40	6
Feverish feeling	2	6	6	0	2	6	38	13
Nausea	9	0	23	13	4	0	34	0
Muscle spasm	0	0	17	0	0	0	17	0
Tremulousness	2	0	15	0	2	6	21	0
Loose stools	2	0	0	6	2	0	23	6
Abdominal distress	0	6	9	13	2	6	36	0
Stuffy nose	2	0	2	6	2	0	11	0
Hiccups	0	0	0	0	2	0	17	0
Wild dreams	0	6	0	0	0	0	19	0

THC = 47 subjects; CBD = 15 subjects

to four days. Disturbed sleep, characterized mainly by increased dreaming and restlessness, was reported by some subjects for up to two to three weeks postdrug.

As predicted by the general principles determining dependence, the greater the dose (30 mg vs 20 mg) and the more frequent (every 3 hr vs every 4 hr), the more intense the withdrawal reaction. Withdrawal symptoms did not appear in two subjects given 10 mg doses of THC every 3 hr for 10 days. At least five days of steady intoxication seemed necessary to produce a minimal withdrawal syndrome. The longer the period of intoxication (up to the 21-day limit of the study), the greater the withdrawal intensity. The six subjects who went through a second cycle of THC administration and withdrawal over a six-week period showed what appeared to be more rapid re-acquisition of tolerance and more intense abstinence reaction on the second cycle. Subjects treated with CBD rather than THC over similar periods of time had no subjective or physiological changes when switched from CBD to placebo. The postdrug latency of the changes in the subjects who had received THC was invariant despite differing periods of hospitalization. This indicates that what we observed was not a result of hospitalization, impending discharge, or other similar nonpharmacological factors.

Summary of Oral THC Dependence Study

In summary, when tested under optimal conditions, cannabis and THC clearly were associated with the fairly rapid development of dependence. Dependence was evident in physiological, subjective, and behavioral indices. The general spectrum of signs and symptoms was consistent with that which appeared postdrug in studies where subjects had selected their own doses of smoked cannabis and with some of the signs and symptoms described in the clinical and field study reports of possible dependence.

Cross-Dependence

Since, according to criteria recommended by the World Health Organization (WHO Scientific Group, 1975), cross-tolerance and cross-dependence between new compounds and opiates may predict opiate-like addiction liability, it is appropriate to consider cross-dependence between THC and other drugs. In animal experiments it was found that the administration of THC diminished some signs of naloxone-precipitated morphine abstinence (Hine *et al.*, 1975; Bhargava, 1976, 1978). THC and nabilone reduced abstinence phenomena in alcohol-dependent mice, though at higher doses of THC, seizures were intensified (Sprague and Craigmill, 1978).

In early clinical trials, pyrahexyl (synhexyl) was thought to be useful for alleviating abstinence signs and symptoms in withdrawing alcoholics and opiate addicts (Thompson and Proctor, 1953). Oral 15 mg doses given three times a day for three to five days were particularly effective in relieving autonomic symptoms and improving mood. The pyrahexyl seemed to be more effective as a treatment for alcohol withdrawal than for opiate withdrawal. Chopra and Jandu (1976) reported that alcohol lessened the intensity of cannabis abstinence symptoms.

If tolerance and dependence are indeed two aspects of the same compensatory process, then these findings are consistent with our clinical observations (Jones and Stone, 1970) that in groups of very frequent marihuana users the most frequent users showed less behavioral and motor impairment than expected after consuming the equivalent of about four to five ounces of 50% ethyl alcohol. MacAvoy and Marks (1975) also found experienced cannabis users to be less impaired by ethanol than nonusers were, on an attention task. In our studies of THC-dependent volunteers, we did not note evidence for cross-tolerance to oral and i.v. ethanol, though there was suggestive evidence based on subjective reports that the ethanol administered after a period of prolonged THC administration did partially alleviate some of the subjective symptoms that we thought represented THC withdrawal (Benowitz and Jones, 1977b).

Does Drug-Seeking Behavior Change with Tolerance or Dependence?

This is an important question that unfortunately is not answered by any of the human studies. We did not measure cannabis self-administration in our studies, since that would have interfered with answering some of the other primary questions. Likewise, in the controlled studies of voluntary *self-administration* of cannabis smoke, the development of tolerance to THC was not independently manipulated or in some cases even independently measured other than by assessing the amount of material smoked and its effects. The design of those experiments was such that nothing can be said about smoking during the abstinence state.

In the ideal experiment, one would wish to learn not only how level of consumption affects the development of tolerance and dependence, but also how tolerance and dependence affect consumption. Both issues have been dealt with separately, to some extent, but what is really required is a single experiment in which levels of tolerance and dependence are manipulated by some means other than voluntary smoking of cannabis (e.g., by obligatory oral doses of THC), and the effect on self-administration of cannabis smoke is then measured. It is faulty reasoning and poor experimental design to allow the subject's self-selected dosage to determine the level of tolerance produced, and then use the level of consumption as evidence of tolerance. In such an experiment, the self-selected dosage is being used as both the independent and the primary dependent variable, an inadmissible procedure.

For example, in the McLean studies (Babor *et al.*, 1975; Mendelson *et al.*, 1976a, b, c) cannabis smoking was measured in groups of moderate and frequent users who, by performing a simple operant task, could earn money that could then be kept or used to buy marihuana cigarettes. All of the moderate and most of the heavier users increased their cannabis consumption, at least as measured by numbers of cigarettes smoked, during the three-week period. The moderate users' subjective intoxication ratings progressively declined with daily smoking while the heavier users' ratings diminished significantly. Such a pattern of change suggests that tolerance develops to cannabis' subjective effects and that this determined the level of cannabis consumption. However, in these experiments, which were not designed primarily to test this hypothesis, allowing the subjects to smoke cannabis voluntarily made for less than optimal conditions for tolerance to develop. At the same time, the increases in numbers of cigarettes smoked could represent any number of nonpharmacological factors, such as boredom, group dynamic influences, and interactions between subjects and research staff. The enormous increases in numbers of cigarettes smoked during the last day or so of the study obviously suggest how environmental-situational considerations can determine the amount smoked.

Fortunately, or unfortunately, the understanding of relationships between tolerance and dependence and the self-administration of other drugs is not much different from what it is with cannabis. Cappell and LeBlanc (1979) make the point that, although it is generally assumed that there is a lawful relationship between consumption of a psychoactive drug and development of tolerance or appearance of withdrawal symptoms, both laboratory and clinical data supporting these assumptions are such that one must make a great leap of faith to accept the notion. They point out that, with the exception of a few opiate investigations, the experimental designs of drug self-administration studies have rarely incorporated self-administration as a *dependent* variable and then independently manipulated tolerance or the timing and severity of abstinence. These authors cite cannabis as a particularly good example, where the relationships between tolerance, dependence, and drug consumption have not been adequately tested experimentally, even though these relationships have been the subject of much discussion and speculation.

With cannabis, as with many psychoactive drugs, a basic assumption is that some effects of the drug positively reinforce its use and that repeated use in a situation in which tolerance develops may produce tolerance to the positive reinforcement. While there are some data (mostly from opiate experiments) in the literature to support this assumption, studies such as those of Woods and his associates (Downs *et al.*, 1975; Woods and Carney, 1978) have been unable to show tolerance to the reinforcing effects of several drugs, as measured by self-administration, even though substantial tolerance to many of the other drug effects (primarily aversive ones) was clearly present. The results of studies reviewed in those articles suggest that, although a relationship between the development of tolerance and dependence and drug reinforcement has intuitive appeal, tolerance to drug reinforcement has not been satisfactorily demonstrated with a number of popular psychoactive drugs. Even the evidence that tolerance influences narcotic drug self-administration is mostly indirect.

Cappell and LeBlanc (1979) also point out that there have been relatively few manipulations of physical dependence as an independent variable, with changes in drug self-administration measured as a consequence. The few existing studies have focused on opiates. Measurements of withdrawal signs and of alcohol consumption, for example, are separated in time to the extent that one would have to conclude that physical dependence on alcohol does not necessarily influence ethanol self-administration. In reviewing the evidence, Cappell and LeBlanc speculate that perhaps cognitive processes unique to humans are necessary to link experienced craving for a drug, the drug effects, the appearance of physical dependence, and its alleviation by further self-administration.

Assuming there are links between tolerance and physical dependence that may reflect operations of common mechanisms (Kalant *et al.*, 1971), some investigators argue that the tolerant cannabis user may increase consumption to offset diminished positive reinforcement. Likewise, the tolerant and *dependent* cannabis user may maintain usage at some optimal level or increase it to alleviate or avoid withdrawal symptoms. Of course, in the real world of drug use, where tolerance and dependence are interacting and occurring simultaneously, one may well wind up with a rather complicated situation analogous to the "titration hypothesis" of chronic nicotine use which is surprisingly popular in the tobacco literature yet has rarely been demonstrated conclusively in experimental studies. That is, a tolerant and dependent user may self-administer a drug to maintain some fairly constant and individually characteristic brain level necessary to produce the pharmacological effects desired (positive effects) and to avoid the unpleasant consequences of abstinence that may occur with falling blood/brain levels of the drug (negative effects). The observations of selected users (Heinemann, 1973) and the pattern of gradually increasing cannabis doses and potency over the past 10 years in Western countries are consistent with a link between tolerance, dependence and drug-seeking. Of course, economic considerations, setting, etc., interact with drug self-administration in a way such as to make any relationship between drug-seeking behavior and a given level of tolerance or dependence most complicated (Edwards, 1974, 1976; Halikas *et al.*, 1978).

Dependence: Evidence from Semi-Controlled Studies

Small groups of selected chronic cannabis users from Jamaica and Costa Rica were said not to show evidence of dependence even after years of heavy use, though "heavy" in the Costa Rican study meant as little as 400 mg marihuana/day in some cases (Rubin and Comitas, 1975; Coggins, 1976; Coggins *et al.*, 1976; Comitas, 1976). However, some physiological measures from the Costa Rica study suggest that the laboratory testing of users was done at a time when some subjects might have been experiencing symptoms of abstinence (Karacan *et al.*, 1976; Dawson *et al.*, 1977).

Costa Rica—Sleep EEG Rebound

The Costa Rica study involved a matched pair sample of 82 people. Forty-one were nonusers of cannabis and 41 were regular users who smoked between 2 and 23 marihuana cigarettes per day with a median of seven cigarettes. They had been using marihuana for 10 to 27 yr. The potency of the Costa Rican marihuana appears to be high, between 1% and almost 4% THC, with the average cigarette containing about 200 mg. In sleep EEG studies, the users had a moderate prolongation of sleep onset latency and slight elevation in the percentage of time spent in rapid eye movement sleep and the length of the rapid eye movement sleep periods (Karacan *et al.*, 1976). The users had EEG sleep characteristics similar to those on the first post-THC night in controlled laboratory experiments in which known doses of cannabis extract and THC were administered under controlled conditions and the effects of the drugs' withdrawal studied (Feinberg *et al.*, 1975, 1976; Jones *et al.*, 1981). A number of other outpatient studies also have demonstrated cannabis effects on sleep (Barratt *et al.*, 1974) and rebound-like changes in the sleep EEG after brief exposure to smoked cannabis or oral THC (Freemon, 1972, 1974; Kales *et al.*, 1972; Pivik *et al.*, 1972; Freemon and Al-Marashi, 1977).

In the Costa Rica studies, users continued their usual marihuana smoking during the day of each experiment. They did not smoke for at least 2 hr before going to bed on the sleep EEG recording nights. This drug-free period would allow for the appearance of changes in the EEG related to abstinence from THC, since Feinberg *et al.* (1975, 1976) found the onset of changes 2 or 3 hr after the last dose of oral THC. Although the investigators in the Costa Rica study did not think the sleep EEG differences in users represented physiological withdrawal symptoms, they did speculate about the possibility and had no good alternative interpretation.

Eye Physiology

In studies of visual function and visual system physiology with the same group of Costa Rican marihuana users and nonusers, differences between users and nonusers that were consistent with physiological withdrawal phenomena were noted (Dawson *et al.*, 1977). Although all values were still within normal limits, users at the time of testing had increased tear flow, increased intraocular pressure, and increased photosensitivity when compared with nonusers. The users had arrived at the hospital between 7 and 9 a.m. (at least 3 hr prior to testing) and presumably had been drug-free since the previous evening. Thus one might assume that on average there had been no smoking for about 10 hr before the tests. In our experimental studies of THC dependence (Jones *et al.*, 1981), increased intraocular pressure above pre-THC baseline values was commonly observed during the first 24 hr of abstinence. Although not routinely tested in our studies, many subjects spontaneously mentioned increased tearing and sensitivity to bright lights during the first 24 hr of abstinence. Since one acute effect of cannabis is to decrease lacrimation, it is not unreasonable to interpret increased lacrimation as a rebound effect.

None of these observations clearly documents dependence, but they follow the pattern that one might expect if dependence develops in the real world of cannabis use. At the very least, I interpret the data from other studies as suggestive of the possibility that, in experiments with people or animals, what is measured may represent the effects of *withdrawing* cannabis rather than the effects of cannabis itself.

5. SUMMARY

Cannabis would be a truly remarkable psychoactive drug if tolerance did not develop to many of its effects (Jones *et al.*, 1976, 1981; Wikler, 1976; Hollister, 1979). Tolerance to most THC effects has been repeatedly demonstrated, both in animals and in humans. Tolerance develops rapidly to what many would consider surprisingly small doses. For many effects, tolerance disappears equally rapidly. There is a little more uncertainty as to the precise rate of disappearance of tolerance in different physiological systems or species, since systematic studies on tolerance loss have rarely been done. The degree of tolerance that can develop is enormous, exceeding that produced by opiates. Many characteristics of tolerance to THC are similar to those of tolerance to opiates, nicotine, and cocaine.

Dependence, both physical and psychological, for those who like to make that distinction, can develop rapidly in animals and in humans. The withdrawal syndrome is similar to that produced by low doses of opiates, alcohol, and other sedatives when they have been given for relatively short periods of time. Similarities between opiates and cannabis, both as to effects and possible shared mechanisms of action, suggest that traditional views of drug specificity in some matters related to dependence and tolerance may no longer hold. Be it opiates, sedatives, or cannabis, there may be more in common than traditional dogma and WHO classifications would indicate.

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Epidemiology of Cannabis in Developing Countries

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1. INTRODUCTION

Virtually no studies of cannabis fitting the classical concept of the word "epidemiology" have been carried out and reported in the world literature from developing countries in Africa and Asia. The reasons for this could be many. The first and foremost would be lack of trained manpower to plan and carry out such studies. Secondly, a relatively low priority is attached to this topic by the Governments of those countries, which have moved only to the minimum extent under the Geneva Single Convention (1961) in the area of enforcement and to furnish guesstimates of prevalence of cannabis use, which surely would be readily accessible to all scientists. Lastly, many investigators have been diffident to report in the scientific literature. Instead, they have published monographs locally.

The concept of developing countries itself is fluid and subject to rapid change. This paper refers to data from countries in Asia and Africa where the life is still primarily agrarian. Industrialization and the changes associated with it have not disrupted the traditional patterns and values that still govern day-to-day living.

The data base is rather too small and the epidemiological studies too scanty to permit broad generalizations about developing countries. In organizing this paper, I will deal firstly with studies on a country/region basis and subsequently will attempt to synthesize the available data.

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TABLE 1

Studies on Epidemiology of Cannabis Use

Location	Field of study	N	Age range (years)	Sampling Procedure	Prevalence Rate	Reference
AFRICA						
Nigeria	Associated socio-psychiatric problems	13	10–34	Purposive, male patients	Not reported	Asuni (1964)
Ghana	Control methods	16	18–31	Purposive	Not reported	Sagoe (1966)
West Africa	Associated medical and social problems	Not reported	–	Stratified, industrial workers and general population	17.5%	Lambo (1965)
Zaire	University students	234	–	Random, second year educational science students	Not reported	Verbeke and Corin (1976)

Egypt	General population	253	15 and above	Stratified purposive	Not reported	Soueif (1967)
Egypt	Behavior	850	15 and above	Purposive, males convicted for hashish use	Not reported	Soueif (1972)
Egypt	Associated psychological deficits	850	15 and above	Purposive, males convicted for hashish use	Not reported	Soueif (1976)
Egypt	Analysis of objective test results	850	–	–	–	Soueif (1975)
ASIA						
Afghanistan *Kabul*	Associated psychiatric problems	775	–	Purposive, patients attending Sanayee Hospital	13%	Gobar (1976)
Nepal	General	226	–	Purposive random	Not reported	Sharma (1975)

TABLE 1 (CONTINUED)

Location	Field of study	N	Age range (years)	Sampling Procedure	Prevalence Rate	Reference
Philippines *Manila*	College students	473	15–28	Quota technique	6%	Zarco (1972a)
Manila	Contrast epidemiological factors of upper and lower class abusers	210	–	Purposive	–	Zarco (1972b)
Five cities in Philippines	Students	2,048	–	Purposive	12.71%	Zarco (1975)
India *Bombay*	Case reports	3	–	Purposive	–	Ewens (1904)
All-Indian States	Long-term cannabis users	1,238	–	Purposive	–	Chopra and Chopra (1939)
Agra	Health and mental disorder	29,468	–	Total population of Agra	4.95%	Dube and Handa (1967)

Uttar Pradesh	General	–	–	Purposive	2.7%	Dube (1972)
Ranchi Mental Hospital	Cannabis psychosis	1,284	–	Purposive	–	Varma (1972)
Lucknow	Bhang psychosis	4	–	Purposive	–	Thacore (1973)
Calcutta	*Psycho-clinical aspects*	*124*	–	*Purposive*	–	*Chopra (1973)*
Bombay	Students	–	18–21	Not specified	17%	Chitnis (1974)
Patiala	Medical students	–	–	–	11%	Singh and Singh (1979)
Delhi	Senior high school	225	14–16	Stratified random	12%	Mohan *et al.* (1978)
Delhi	–	1,118	17–20	Stratified random	2.61%	Mohan *et al.* (1978b)
Lucknow	Motivational factors	40	–	Random purposive	–	Sethi *et al.* (1975)
Military Hospital	Cannabis psychosis	334	–	Total patient population in a military psychiatric centre over an 8-mo period	14.4%	Goel and D'Netto (1976)

TABLE 1 (CONTINUED)

Location	Field of study	N	Age range (years)	Sampling Procedure	Prevalence Rate	Reference
Madurai	Cognition	34	–	Purposive, males only	–	Venkoba Rao (1976)
Delhi	Students	1,135	14–20	Total coverage two institutions	5%	Mohan and Arora (1976)
Punjab	General	3,600	above 15 years	Two stage design	1.2%	Mohan *et al.* (1979a)
–	Medical students	50	–	Voluntary subjects	–	Chawla *et al.* (1975)
Chandigarh, Punjab	Students	550	16–20	Not specified	2%	Varma (1977)
Lucknow, Uttar Pradesh	Medical students	900	17–21	Not specified	14.9%	Sethi and Manchanda (1977)
Agra, Uttar Pradesh	Medical students	1,100	17–21	Not specified	36.82%	Dube (1972)

Punjab	Psychological correlates	–	–	Purposive, males only	–	*Mendhiratta *et al.* (1978)
Punjab	Effect on cognition	–	–	Purposive	–	*Wig and Varma
Haryana	Psycho-social correlates	–	25–50	Purposive, rural areas, males only	–	*Ray *et al.* (1978)
Haryana	Cognitive functions	–	–	Purposive, rural areas, males only	–	*Ray *et al.* (1979)
Punjab	Prevalence in rural area	–	15–19	Systematic random, rural areas, males only	0.8%	*Mohan *et al.* (1978a)
Chandigarh, Punjab	School and college	–	15–20	–	52.4% all drugs	Varma and Dang (1979)
Punjab	General population	701	10 +	Systematic random	29.98%	Lal and Singh (1979)
Ajmer Rajasthan	General (rural)	4,670	–	Two stage design	4.0%	Mohan *et al.* (1979c)

2. STUDIES IN CENTRAL AFRICA

Nigeria

On reviewing some of the published articles in Africa, one runs into the difficulty of getting hard data, but has the impression that the cannabis problem is growing. Asuni (1964) referred to increasing *seizures of illicit cannabis* as evidence for its increased use. The plant is not native to Nigeria, and was probably introduced to the country by military personnel in World War II who were returning home from the Middle East, the Far East, and North Africa. It was Asuni's impression that "the local users of cannabis are usually found amongst the lower class—mostly in towns. There is no evidence that there is a positive correlation between poverty and cannabis smoking." Cannabis smoking was slowly gaining respectability among other social groups. The drug use was spread by peer group pressures, and public attitudes towards its use varied. In analyzing the clinical data, Asuni found that most of the users seen professionally by him belonged to the transitional group, making a move from rural to urban areas. They were diagnosed as psychotic (16 Ss) and neurotic (six). Cannabis use did not appear to be causally related to their illness, though it seemed to have precipitated the symptoms. The addiction potential of Indian hemp was judged to be fairly low. Regarding its social effects, Asuni observed that in due course there was a definite downward drift associated with cannabis use, leading to a user's reduced social status, ultimate unemployment, and movement to a "fringe group." Cannabis use also reduced the cohesiveness of the family. In concluding, he remarks that "if occupation may be used as an index of acculturation or departure from the controlling influence of traditional and indigenous means and ways of life, it becomes quite obvious that most of the people who are smoking Indian hemp, are those who have grown away from this influence."

Lambo (1965) covered similar ground from a West African perspective. Six significant variables associated with the use of cannabis were identified. Young single male migrant workers, who were moving over West Africa in search of jobs in urban areas, constituted the biggest single group vulnerable to drug abuse. Life was difficult for these migrant groups and many of them had maladaptive lifestyles, which led to neuroses, delinquency, and drug-taking, primarily as a coping device. Lambo felt that the assumption that drug use primarily led to mental illness with which other sociopathological phenomena *covaried* was probably false. In a way, drug use and mental illness might themselves be symptomatic of the disintegration of traditionally supported kinship groups, leading to social isolation along with economic deterioration. Lambo's viewpoint reflected the "contagion" theory of spread of drug use and echoed Durkheim's concept of anomie, with all its nuances and meanings. Lambo contrasted the urban chaos with rural stability. Among factors contributing to drug use in general and cannabis use in particular, he first pointed to vast migrations within national or international boundaries, and activities such as tourism and ancillary services which developed with them. Construction projects attracted seasonal migrant workers. The second factor was socioeconomic, related to population shifts. The areas of relatively high economic level attracted the "fringe groups," among whom cannabis intake started. He advanced the concept that in developing countries, drug abuse should not be understood only as individual proneness, but as a part of larger socioeconomic change, rising populations, and greater expectations from society which somehow remained unfulfilled because of other pressing factors. Lambo found that users tended to seek each other out and form typical subcultures with their own norms. Since the population between the ages of 15 and 45 yr was large, with many school drop-outs, many adolescents were involved in cannabis smoking. No distinctive personality profile of chronic cannabis abuse was noticed. However, where cannabis was used in combination with alcohol, personality disintegrated early. The statistics of crime related to cannabis use compiled from the police, official records, and other sources revealed that about 50% of the respondents were involved in murder, assault and battery, sex offences, fraud, indolence, and excessive drinking.

Zaire

Verbeke and Corin (1976) state that in Zaire, cannabis use was common among idle delinquent youth especially in an urban milieu, musicians, the military, and senior citizens in rural areas. The occasions of use were celebrations, war, and, among delinquents, as a preparation for the commission of crime. The motives for use were to suppress fear and to acquire energy and endurance for arduous tasks. What stood out in their study was that cannabis was used in a functional manner for specific situations rather than for merely recreational purposes.

From a review of the published literature from Central Africa, the main impressions are: (i) Cannabis smoking is a comparatively recent phenomenon, beginning at the end of World War II; (ii) Its use is largely confined to the migrant urban male adult population; (iii) It is also used by certain occupational groups, such as lorry or taxi drivers; (iv) Incipient use is present among young school or college student populations; and (v) Unlike countries of Asia and the Southeast Asian region, where cannabis use is by and large for recreation and relaxation, African countries show a pattern of cannabis indulgence associated with situations calling for aggressive postures and violence. Similar views are by and large expressed by Sagoe (1966) who studied narcotics control in

Ghana. None of the studies reviewed made any reference to other cannabis effects, such as "flashback phenomena" or cognitive deficits.

3. STUDIES IN EGYPT

Soueif (1967, 1971, 1972, 1975, 1976, 1977) has thrown some light on the problem of cannabis abuse in Egypt. His studies were not epidemiological, but were more similar to a case-control design, in that they tended to focus in depth on long-term effects of cannabis use. Observations are made about cannabis use in the sample. In his earliest study, Soueif (1967) describes the construction of a questionnaire that could serve to study other long-term cannabis users. Based on the above study, certain tentative conclusions were drawn. Hashish use appeared to be negatively associated with work. There was a definite deterioration of work performance in long-term users. The hashish habit was more common among the unmarried, divorced, and widowed than among married persons.

Most of the cannabis users in the 1967 Soueif study took it at a set time, in the company of other users. The reasons for taking hashish or discontinuing its use were also mentioned but this information was less reliable. Children of hashish smokers were more likely to smoke hashish than were those of nonsmokers. Regarding the effect of cannabis on users, Soueif says "there is a definite pattern of oscillation of temperamental traits, swinging between two opposite poles, that of social ease, a desire to mix [with others], acquiescence, elation, and agreeableness... when under immediate drug-effect and that of ascendency, seclusiveness, negativism, depression of mood, and pugnacity . . . when subjects are deprived of the drug." Several cognitive effects, such as inaccurate time perception, lengthening of distances, enlargement of object sizes, and brightening of colors were reported by users under the influence of cannabis. A sizeable proportion also reported impaired memory for recent events. Productivity was lowered, both during the time when people were under the effect of the drug and when they were not under its influence but craving for it. Though no prevalence estimates were offered, based on the amount of confiscated hashish destined for domestic consumption, Soueif calculated that the number of "habitués" could be around 180,000, the majority of them in the age group 20–40 yr. The main aim of this study was to devise tools and techniques for surveys of hashish users, and to train the interviewers to ensure greater validity and reliability. Thus the major contribution of this communication was the evolution of an itemized instrument for use in the study of hashish users and controls.

The second study by Soueif (1971) included more subjects and the use of other experimental techniques. The sample for this study was drawn from prisoners in city and rural jails arrested for hashish smoking (N = 859). The controls were also chosen from the prison population but had not been convicted on hashish charges and had no past history of cannabis use. Soueif remarks that although there were some differences in the experimental and control groups, age and urban/rural backgrounds of the two groups were similar. Members of the experimental group were more likely to be married and had better incomes than members of the control group. All subjects were given the standardized interview schedule constructed earlier (Soueif, 1967). In addition, a battery of psychological tests was administered. These tests involved activities that were commonly known, understood, and relatively independent of any specific culture. All testing took place at one time without any external interference. The duration of testing, including the answering of the questionnaire, was approximately one hour. The usual mode of taking cannabis was smoking. Very few habitués used the oral route and only a small percentage combined smoking with some other route of administration. The users had definite preference concerning the time of day at which they smoked. However, many heavy users (who smoked more than 30 times a month) took it during the morning or afternoon, as well as in the evening while moderate smokers (who smoked 30 times a month, or less) did so only in the evening. This difference was significant, and suggested that the heavy users might be dependent on cannabis. The amount of cannabis intake during a day varied in heavy users and moderate users and ranged between 0.54 and 1.08 g of hashish in 67% of the users (22.4% took less than 0.54 g per day and 10.3% took more than 1.08 g). A larger percentage of moderate users (31.2%) than of heavy users (18.2%) took less than 0.54 g at a time, while a larger proportion of heavy users (13.2%) than of moderate users (4.9%) took more than 1.08 g at a time. City dwellers took much less than rural dwellers.

The heavy and moderate users did not differ with respect to situations in which they started use, or to conscious motives for use. More moderate users than heavy users had made one or more attempts to give it up. Conversely, more heavy than moderate users gave neurotic responses to three selected items from Taylor's manifest anxiety scale. Concomitant opium use was seen in 31.6% (more than previous estimates of 26%), and was more prevalent in heavy smokers than in moderate ones, and in urban subjects than in those from a rural background. More heavy hashish smokers (27.7%) than moderate ones were found to be also using alcohol. Hashish users also used more thick Turkish coffee than controls did. Coffee drinking was more common in city dwellers and in heavy than in moderate smokers of cannabis. Consuming tea and smoking cigarettes were significantly more common among users. The use of other drugs had started before cannabis use was initiated. Heavy users tended to use other drugs more often than moderate users or controls. In the same fashion, the heavy users started consumption at a younger age than the moderate group (Soueif, 1972). As compared with late beginners (28 yr or older), more of those who began use early (16 yr or younger) used it in the morning and afternoon, had history of another user in the family, had one parent dead and the other remarried, or had separated or divorced parents (Soueif, 1971). The motives for and effects of cannabis use were assessed on the basis of subjective reporting. The motives were: to do as their friends were doing (87.8%), to attain euphoria (86.6%), to behave like real men (72.5%), to forget personal problems (42.8%), to obtain a medicinal effect (27.3%), and to increase libido (23.8%). Among the users, the effects reported were euphoria, acquiescence, suggestibility, carefreeness, distortions in perception of time, lengthening of distances, and enlargement of objects or change in their shape. These effects generally were independent of rural/urban background.

On testing, the controls scored better than the experimental group on many tests (e.g., speed and accuracy of psychomotor performance and digits forward and backward). On time estimation, urban takers scored better than controls. In lower Egypt (rural), however, there were few differences between the users and controls. Summarizing the results, Soueif hypothesized that "the effect of learning on speed and accuracy of performing simple psychomotor tasks and on rote memory goes at a slower rate in cannabis takers compared with controls. In other words, cannabis users are slow learners compared to nonusers." Although it was tempting, the author cautioned against concluding that there was a cause and effect relationship between cannabis use and functional deficits, as there was a fairly large number of intervening variables that had not been assessed.

4. STUDIES IN ASIA

If the information and data regarding cannabis use are rather limited for a large continent like Africa, information and data regarding this subject are even more scanty in west Asian and the Middle East countries. At an interregional meeting of countries belonging to the South East Asian and Eastern Mediterranean Regional Offices of the WHO (SEARO and EMRO), even though cannabis was mentioned as a commonly used drug, very few actual study estimates were given (EMRO, 1979).

Fort (1965) presented a wide-ranging subjective view of drug use in Asia (excluding Asian portions of USSR, Turkey, Syria, Lebanon, Jordan, Israel, Arabian Peninsula, and China). The major psychoactive drugs used in the area were opium, heroin, cannabis, and alcohol, but in several countries there was considerable use of psychotropics and indigenous substances. The region is itself socioeconomically backward and underdeveloped, and typical users came from the lower classes and were uneducated. Generally the drug users were males ranging between 15 and 50 years of age. In many countries use was traditional and socially tolerated, although actual laws usually reflected "western values" on this subject. All users of narcotics were referred to, or dealt with, as drug-dependent, although many of them used these agents intermittently and were not dependent pharmacologically. Cannabis was known in China as early as 2730 B.C. and was described in the pharmacopoeia, where it was labeled as "Liberator of Sin." It was used not only for its euphoric properties, but also as a medicine for diseases such as arthritis and malaria.

Cannabis use has been known in India since 800 B.C. The origin of the term "Indian hemp" remains unknown, but its cultivation and use became almost a science. In contemporary India, the author estimates that users of both cannabis and opium number roughly 1,000,000, though official estimates are 200,000 of each. The present situation in Pakistan probably parallels the Indian estimates proportionately. The use of cannabis seems to persist in Northeast Thailand, Burma, and in Sri Lanka, although on a much more restricted scale. No figures, however, can be cited to support this opinion.

Afghanistan

Gobar (1976) reviewed the drug use problems in Afghanistan, relying on hospital admission records of 5,779 persons between 1960 and 1969. The hashish smokers constituted about 13% of all hospital admissions. Use was confined to adult males of lower socioeconomic strata, hermits, and "less orthodox clergymen" who wanted to achieve mystical experiences. The cannabis plant was often called "bothae faquir," i.e., "hermit's plant." The author claimed that, in his culture, smoking of cannabis was often identified with insanity and its use discouraged. Clinically he did not describe any adverse effects associated with cannabis use, though occasionally patients who became delirious after cannabis intake were seen in the hospital.

Nepal

Sharma (1975) described 226 cannabis users from Nepal who were matched for age, sex, and education with an equal number of controls. His study did not have any quantitative measures, but on comparison with controls, all the users came out as poor seconds on general behavior, personal hygiene, work, and occupation, and their conversation was more self-centered than that of controls. They were low in libido as well as in sexual performance. They did not have a criminal history, and were found in general to be more quiet, docile, and religious.

India

In India, cannabis use has been studied since 1893, though few epidemiological studies have been carried out. The most exhaustive and early survey was carried out by the Indian Hemp Drugs Commission (1893–1894). The report consisted of written and oral examination of 1,193 witnesses, and direct observation of areas of cannabis cultivation, the processes involved in manufacture of its derivatives, and the religious centers and other places in the region where it was supposed to be used maximally. It included all the countries which were then a part of British India, viz. India, Pakistan, Bangladesh, Burma, and Sri Lanka. The Commission found that *Cannabis indica* was not indigenous to India but was probably imported from Iran. The female plant was grown from Kashmir to Assam in the foot-hills of the Himalayan belt for producing fibres, but it could also produce charas or ganja. It also grew wild, down the Ganges valley. At that time, 6,000 acres were harvested for drug use and 1,500 acres for the fibres. The main cannabis drugs recognized by the Commission were:

(i) *Bhang:* Also known as "siddhi," "patti," or other colloquial names; these terms referred to the leaves of the plant, male or female, cultivated or wild.

(ii) *Ganja:* The name given to the dried flowering tops of cultivated female plants, which become coated with resinous material. Since male plants are destroyed early, the female flowers are not fertilized and the plant produces more flowers and resin.

(iii) *Charas:* The name given to the collected resinous exudate from the plant.

The Commission did not give any estimates of consumers at the national level, but gave a range of 0.5%–1.0% of the populations of individual provinces as being habitual cannabis users. They estimated the number of individual consumers by dividing each population by excise estimates of the sale of ganja or charas within the respective province. Since bhang was not an item of excise control, its use was not estimated by the Commission. The Commission also did not arrive at definite levels of dosages consumed daily, that could serve as cut-off points between normal moderate use and heavy or excessive use, since the amounts typically consumed varied from province to province. Discussing the issue of moderate and excessive use, the Commission compared ganja with alcohol. It also looked at the possible dependence potential of ganja vis-à-vis alcohol. It concluded that moderate users of ganja did not automatically increase the amount consumed over a period of time, as alcohol users did. According to evidence presented to the Commission, no conclusions could be drawn regarding adverse effects on individual users.

Mental Effects

The mental effects of cannabis were summarized by the Commission, and compared with those of alcohol. The four effects noticed were:

(i) *Hemp drug intoxication*—the condition of more or less delirium with hallucinations and merriment, occurring in those who had taken what was for them a large dose of the drug. The symptoms were purely temporary;

(ii) *Hemp drug delirium*—the condition of wild frenzy with symptoms of transitory mania occurring in a person who had systematically indulged heavily in the hemp drugs;

(iii) Cases where the drug had been used for a considerable period, and then gave rise to mania of shorter or longer duration, or cases in which the symptoms of hemp drug delirium did not completely subside, but passed into a state of mania that was usually curable, thus indicating the probable absence of an anatomical lesion;

(iv) The Commission did not find sufficient evidence to link cannabis use to a case of typical insanity.

In summarizing, the Commission came to the conclusion that occasional and moderate use of hemp drugs might be beneficial, indeed it could be medicinal. Regarding effects on physical state, in moderate doses there were no ill effects. The excessive use, as with any intoxicant, might be harmful. The injurious effects of moderate doses on the mind were not serious but in susceptible individuals even moderate use might precipitate mental illness. It also concluded that use of moderate doses did not have any "moral" effects, such as might be found in users of excessive doses. These effects were primarily on the individual and did not affect the society at large, as cannabis indulgence seldom resulted in criminal activity.

The two Indian members of the Commission, however, gave a minority opinion, stating that the Commission had not distinguished clearly the harmful effects of ganja and charas from those of bhang, and that taxation as an instrument for reducing consumption was not likely to meet with success. This could only be achieved by applying prohibition measures gradually from charas down to bhang in a phased manner.

Within a decade of the report of the Indian Hemp Drugs Commission, the first of two Indian psychiatrists presented clinical material that contradicted its findings. Ewens (1904), after careful review of all the patients seen by him, described hemp drug insanity as a violent or sudden mania, with intervals of great excitement and great exaltation of ideas. Initially, he said, there was a tendency to perform impulsive acts of violence and destruction, with a total loss of memory for these events and for all but the commencement of the symptoms. The patients usually showed rapid recovery on stopping use of the drug, but occasionally the symptoms could be prolonged.

Dhunjibhoy (1930) described the clinical picture of hemp psychosis produced by excessive or prolonged moderate use of the hemp drug in any form. Its prevalence was higher in Punjab, Bihar, Orissa, and Bengal. The drug use was almost always among men between 20 and 40 yr of age. He identified three varieties of cannabis psychosis: acute mania, chronic mania, and dementia.

(i) *Acute mania:* This was the result of prolonged use of any form of cannabis drug. It presented with features of mania and, in addition, visual and auditory hallucinations. The duration of the attack was short but relapses were common, with complete amnesia for the whole episode. Congestion of the eyes, a characteristic daredevil demeanor, and absence of psychopathic or neuropathic heredity were observed.

(ii) *Chronic mania:* The clinical picture was the same as above but, in addition, the patients were jocular and boastful, with a sense of well-being. A very rare symptom was complete loss of speech, lasting for long periods after recovery from the illness.

(iii) *Dementia:* If untreated, a small number of the individuals progressed from chronic mania to dementia.

Chopra and Chopra (1939) reported on data from 1,238 long-term cannabis users. Though the sample covered all states in the country, it was not representative of the whole population. The report was closer to a case study than to an epidemiological survey. Apart from an assessment of sociodemographic factors, the study included a good general physical examination of the subjects, but no psychological tests were used. Of the 1,238 users, 772 used bhang and 466 used either ganja or charas. The oral route for taking bhang and ganja was more common among the Hindus, while charas smoking was more prevalent among the Muslims. More than one-third of the respondents had a family history of drug use by one or more members. A little less than 50% gave a history of psychological illness, such as neurotic traits, sleep disturbances, and irritability. Treatment of these complaints was also often cited as a reason for initiating cannabis use, and these subjects claimed all-round improvement with the drug. The majority started use of cannabis between the ages of 21 and 40 yr. Twenty-nine percent were religious fakirs, 24% laborers and artisans, 15% were tonga drivers, and 9% were Brahmins. Ganja and charas were more commonly used among the younger age groups. The reasons stated for use were the solving of religious or emotional conflicts, the seeking of euphoria or as a substitute drug on withdrawal from addictions to opium, alcohol, or other drugs. Cannabis use was, by and large, a group activity. When given by the oral route, the drug produced a mild sense of euphoria lasting for some time. With smoking, the action was quicker in onset and of longer duration. The majority of bhang users took around 2,700 mg per day or less, while those smoking ganja or charas generally took more. The duration of habit in the bhang users ranged from 1–25 yr. Very few started its use in their forties or later. In assessing the effects, the authors relied heavily on the subjective experiences of the respondents. For those who took bhang in moderate doses, the subjective feeling was one of well-being, relief from tensions and worries, good appetite, and sound sleep. Objectively, they were emotionally labile and had impaired judgment. The effects appeared about half an hour after drug intake and lasted for a variable period of time. The morning after, they experienced slight hangover and redness of the eyes. On the other hand, ganja or charas, when smoked, initially produced anxiety and restlessness, followed by a sense of well-being, convivial mood, overtalkativeness, and hyperactivity. Objectively, the same features as observed in bhang users were seen. Distortion of time and space was experienced by most; labile affect and impaired judgment were followed by sleep. The effects varied with the dose and some atypical responses were seen.

Objectively, the observations lose significance because controls were not described. Bhang users and ganja/charas smokers were not comparable because they differed in the route of intake as well as in the amounts of concomitant tobacco use. In addition, the absorbed amount of the active principle of the drug varied. In spite of all the shortcomings, the results did show that bhang users were less affected than ganja users and charas users; and that some of the effects experienced might be due to the drug itself.

The authors' major conclusions were: (i) Moderate doses of cannabis either for medicinal or habitual use had no appreciable harmful physical effects. Heavy use by smoking caused bronchitis and chest infection; (ii) Moderate use was not causally connected to development of insanity; (iii) Cannabis use was not associated with any "moral" degradation though it might lead to disowning of the user by his own social group.

Chopra and Chopra (1965) summarized their earlier studies and updated them, suggesting revised estimates of the numbers of users, without taking into account the partition of the country in 1948 and the population growth. These estimates were probably low, though Chopra

(1969) subsequently revised the estimate of cannabis users to around 300,000.

The conclusions and recommendations of the Indian Hemp Drugs Commission and of the above study need careful evaluation in terms of their applicability in the modern context. Kalant (1972) suggested that contemporary issues could be looked at from three angles. First, the Indian Hemp Drugs Commission report could be seen as a model or prototype of a method for investigating complex social issues and phenomena. Secondly, the effects of the drug, especially the physical and mental ones, should be re-evaluated in the light of modern knowledge. Lastly, it must be mentioned that the Hemp Drugs Commission recommendations were made in a given sociopolitical climate then prevailing in the region, and did not necessarily apply to other cultures and other times.

Dube and Handa (1969) looked at the prevalence of drug habits among normal and psychiatric patients. They concluded that normal individuals tended to be discreet in their choice of drugs while the mentally ill showed multiple drug use. In the mentally ill, especially schizophrenics and manic-depressive psychotics, polydrug use was common, including that of bhang, ganja, alcohol, and opium.

Varma (1972) reported on cannabis use after scrutinizing the records of the admissions to a public mental hospital during the period of 1959–1969. Out of a total of 39,001 records, 1,248 cases of psychotic illness were considered to be related to cannabis. It is interesting to note that not a single woman was present in this diagnostic group. The author described insidious personality changes in individuals who were initially industrious, friendly, and social (although inclined to be selfish). They were as proud of their ganja habit as of their health. Slowly they became irritable with flashes of anger and developed a tendency to take umbrage at the slightest real or imagined instances of injustice and grievance. They accused their spouses or family of neglect. As the time passed, their dress became slovenly, and they appeared dishevelled and with dirty hair. Increased carelessness about work and duty was observed. They became unemployed or neglected their business; this led to eventual marital disharmony. The clinical illness passed through three distinct phases.

(i) *The acute anxiety phase:* Acute intoxication in the regular users was characterized by a feeling of lassitude and lightheadedness. The body seemed to be floating in air. The users were disinhibited, happy, and cheerful. The laughter was hilarious but not infectious. The novice users, however, became anxious, restless, and had difficulty sleeping. The symptoms could persist for as long as a week.

(ii) *Acute toxic phase:* This occurred when the regular smoker took more than his customary quota. The onset was abrupt, with pointless hyperactivity, use of filthy vulgar language, inability to recognize familiar persons, and incontinence of bladder and bowel. There was a strong tendency to run away from home. The attention and interest could be aroused but not sustained. Impulsive behavior was marked.

(iii) *Phase three:* The acute toxic phase passed after a few days, leaving the patient in a state of mild excitement, which was not uniform. The general slovenliness persisted. The general mood and behavior kept altering unpredictably. Visual hallucinations were dominant. The religious-minded had visions of their favorite deity. Besides visual and auditory hallucinations, olfactory and tactile hallucinations could also occur. There could be delusions of grandeur as well as delusions of infidelity by the spouse. Orientation was good for persons but not for time and place. Concentration and judgment remained poor. Physical examination revealed the presence of muddy green eyes, sunken eyeballs, emaciation, chronic bronchitis, and diarrhea or constipation. The essential difference between the cannabis psychosis and the functional psychoses (i.e., schizophrenia or manic-depressive psychosis) was the presence of a disturbed sensorium. The study, however, suffered from all the flaws inherent in retrospective data based on hospital records. It was also deficient in that it did not give the history of all other patients who took cannabis and did not develop a psychosis or neurosis. Lastly, the mental hospital in question was located in an area of high cannabis use which would tend to vitiate the results.

Thacore (1973) described four cases of individuals with clear sensorium, all of them males who had been long-term cannabis users and had developed psychoses. The behavioral disturbance was characterized by a hostile perception of the environment, fearfulness, delusions of persecution, and auditory and visual hallucinations. The author therefore concluded that prolonged use/abuse of bhang in susceptible individuals might produce tolerance and induce schizophrenia-like psychoses, which could be called "bhang psychoses" and had good prognosis.

Chopra (1973) presented his observations on the psychoclinical aspects of 124 cases of long-term marihuana smokers. Routine physical and neurological assessments were made before and after drug use. The subjects were evaluated on the basis of subjective reports of health status and occupation. The majority (53.2%) felt no adverse effect of the drug on health and work capacity. In 25.6% of cases, health was impaired to a minor degree; 18.5% had marked impairment in health and work; 3.2% reported that their health had improved. Physical and physiological effects included congestion of conjunctivae, dry throat, increased appetite, tachycardia, irritating cough, laryngitis, dyspnea, and, at times, asthma. The psychiatric aspects were studied first with the usual dose and subsequently with an increased dose up to the point of intoxication. Acute psychiatric reactions were infrequent with the regular dose. In higher doses, symptoms of acute intoxication appeared more in those who were susceptible. These symptoms tallied with the observations of Dhunjibhoy (1930) and Varma (1972).

Sethi *et al.* (1975) attempted to assess the motivational factors leading to cannabis use. The authors selected their subjects, bhang users, from one of several bhang shops in the city of Lucknow. A random sample of 40 users was divided into two groups: the traditional (those with a family history of bhang intake) and nontraditional users (negative family history of bhang use). It was hypothesized that the nontraditional group would show greater psychopathology. The two groups were group-matched for age and sex, and for other demographic features except for income and marital status. The mean duration of use was 10.7 yr in the traditional group and 11.4 yr in the nontraditional users. On critical evaluation, 18 out of 22 in the traditional group and 17 out of 28 in the nontraditional group had normal personalities. Symptoms of psychopathology were seen more among the nontraditional users. The most common motivating factors for initiating cannabis use were: for family and religious functions (44%), for obtaining euphoria (18%), and because of peer group pressures (18%). Three persons took it for medical purposes and one as an analgesic. The reasons for continued use fell into three major categories: (i) to obtain emotional release and experience the euphoric effects; (ii) to avoid boredom and fatigue, and (iii) to promote concentration for mental work.

Goel and D'Netto (1975) studied 334 consecutive admissions to a military hospital and questioned those people regarding their cannabis intake at any point in life prior to admission. In all, 14.4% of the patients admitted to cannabis use. Of these, 89.6% were occasional users, 4.2% took it frequently, and 6.2% admitted to being regular users. The clinical picture was one of marked excitement, hyperactivity, circumstantiality, labile mood, excessive religiosity, delusions, and vivid visual hallucinations. They showed euphoria without elation, and flight of ideas. The symptoms did not resemble those of any functional psychoses, being nearer to acute organic brain syndrome. The patients were also to some extent confused and delirious, though routine neurological examination was normal. All but one recovered rapidly.

Chawla *et al.* (1976) studied 50 normal medical student volunteers of both sexes to assess effects on various aspects of cognition after they had been given graduated doses of a cannabis leaf preparation. Of the total, 15 subjects were used for the pilot study, 30 for the final study, and five constituted the negative controls. The pilot study established the dose and the time period necessary for drug effects to appear. In the main study, the test battery was given one day before drug administration to establish base-line norms and was repeated four and a half hours after drug intake. The tests used were Cattel's digits forward and backward, serial subtraction, Cattel's test for thought process, and Cohen and Mozey's test for time perception. The tests for memory and thought showed no abnormality. There was a uniform deterioration on tests of attention and concentration after cannabis intake. Although not statistically significant, there was an expansion in time reproduction. The failure to observe more striking differences was attributed to (i) a sample which was well above average in intelligence and was achievement-oriented, (ii) a limited number of observations, and (iii) a selection of tests which were probably not discriminating enough.

Venkoba Rao *et al.* (1975) reported on cognition and ganja consumption. The study was carried out on a sample of 34 males attending the hospital outpatient department for treatment of psychiatric disorders, who also had a long history of ganja smoking. The psychiatric illnesses were personality disorders, schizophrenic illness, affective psychoses, and anxiety neurosis. Those with toxic confusional states and organic psychoses were excluded. The subjects fell between 15 and 35 yr of age and each served as his own control. The tests given before and after drug intake were (i) attention span, (ii) digits forward and backward, (iii) paired association learning, (iv) visual reproduction, (v) recognition of photographs, and (vi) weight discrimination. The drug-free testing was controlled by restricting the ganja consumption 24 hr before initial testing. The second session was conducted after seven days of normal ganja smoking. The dose smoked was 0.5 g of ganja in cigarettes. Significant drug effects were observed in photograph recognition which improved after drug, as well as in paired learning and weight discrimination errors ($p < .05$). Differences on all other measures were not significant.

Mendhiratta *et al.* (1978) reported on 50 long-term male urban users located by personal contact, 25 of whom were taking cannabis leaf regularly and 25 of whom were smoking charas. They had been habitually taking the drugs for about 10 yr. The average daily dose of cannabis for the bhang drinkers was calculated to be 150 mg of Δ^9–THC, and for the charas smokers 140 mg, on the basis that the leaf had 1% and charas 3% of THC. The control group consisted of 25 psychiatrically normal urban individuals of comparable sex, education, and occupation. They were selected from the poorer strata of society, but had never taken cannabis. A general physical examination of the two groups of users did not reveal any gross pathology, and there was no history of cannabis psychoses among them. The same psychological tests were given by the same persons to all subjects; and an attempt was made to see that cannabis users did not take any cannabis 12 hr before testing. The tests were digit span (forwards and backwards) (taken from the WAIS), symbol recognition, pencil tapping speed and accuracy, Bender Visuo-Motor Gestalt (BVMG) test, Maudsley Personality Inventory (short scale), size estimation, time perception, and reaction time. Charas smokers performed badly on all tests as compared with bhang drinkers or normals. The control group demonstrated the best performance. Charas smokers performed slightly better than bhang drinkers on digit span backward, and the BVMG test. The differences between the charas smokers and the bhang drinkers were significant only on pencil tapping and time perception tests, on which charas smokers performed more poorly. The authors state that a comparison of these findings with those of many other studies of cannabis users was difficult because of variations in duration and dosage, frequency of intake, and the motivational factors. The impairment of time estimation was reported by Soueif (1967, 1972) only in city dwellers. Unlike Soueif's study, this one did not show any emotional instability in cannabis users.

Wig and Varma (1977) reported on a study of 139 long-term heavy users who had taken 1 g of charas or 5 g of cannabis leaf (equivalent to 50 mg Δ^9–THC) per day for five years. Of these, 23 subjects were selected and matched with 11 controls for occupation and marital status. The following tests were given to them: (i) Raven's Progressive Matrices, (ii) Malin's Intelligence Scale of Indian Children, (iii) PGI Memory Scale, (iv) BVMG test, (v) the speed and "H" marking tests from the General Aptitude Test Battery, (vi) a color cancellation test, and (vii) a time perception test.

Compared to nonusers, users obtained significantly lower intelligence and memory quotients and higher Hain's scores on the BVMG test (an indication of cognitive impairment). Users also scored significantly lower on speed marking tests, and made more errors in the perception of time. They also performed more poorly on tests of 'H' marking and color cancellation but the differences were not significant.

Ray *et al.* (1978) reported on psychosocial correlates of chronic cannabis use in 30 rural subjects who had been using cannabis at least 11 times a month for a period of five years or more. The controls were 50 subjects who did not use any drugs and were selected from the general population to which the users belonged. Experimental and control groups had similar age distributions, occupations, and socioeconomic levels. Psychosocial adaptation was assessed by enquiries into areas such as self-aspiration, present occupation, occupational satisfaction, marital status, sexual behavior, self-reported deviant behavior, and future planning for children. On none of the variables were the users different from the controls. Ray *et al.* (1979) also reported on the cognitive functioning in the same groups. The users and controls showed no differences on any tests, except on one subtest of the memory scale.

In examining the research that has gone into the clinical work in India, one can find very little fresh knowledge that has emerged. The studies on long-term effects have yielded contradictory results and have supported the hypothesis advanced by Soueif (1975), i.e., that the differences in performance between users and nonusers are related to education, age, and urbanicity.

Population Surveys

The pattern and prevalence of drug abuse have been studied in recent times in the northern states of the Indian Union, Uttar Pradesh, Punjab, and Rajasthan. Dube (1972), while carrying out a survey of psychiatric morbidity in Uttar Pradesh, found that 2.27% of respondents were drug users. More than 50% of these were users of alcohol and 18% of cannabis, mainly bhang. The rest were users of opium or multiple drugs.

Lal and Singh (1979) surveyed a single village in Punjab with a population of 6,999 persons. By systematic sampling, based on the household as a unit, 108 households with a total of 701 persons were surveyed. Approximately 40% of the sample admitted using tobacco. It was found that 30% of all persons interviewed had taken other psychoactive drugs during their lifetime, giving a prevalence rate of 300/1,000 population. The six-month period prevalence rate for "current" users was 287.7/1,000 population. The population surveyed (above the age of 10 yr) showed a prevalence rate of alcohol use as 25.6%, opium 18.4%, barbiturates 6.2%, and cannabis 2.2%. Some of them also used the above drugs in multiple combinations.

Mohan *et al.* (1978a) used a two-stage sampling design so as to cover about 24 villages in Punjab. The individual households were the basic sampling unit and all individuals above the age of 15 yr were individually interviewed. The total respondents were 2,064 males and 1,536 females. The results showed that the period prevalence rates of use (1 yr) were: alcohol, 58.3%; tobacco, 19.3%; opium, 6.3%, and cannabis, 1.2%. Other psychoactive drugs were not used at all. Multiple drug use with alcohol as a base was common.

Mohan *et al.* (1979c) carried out a survey on drug use in a rural population in the Ajmer district of Rajasthan covering 1,425 households. The basic sampling design and schedules were the same as in the Punjab study (Mohan *et al.*, 1979a). The total respondents were 2,331 males and 2,339 females. The prevalence rates of drug use were tobacco, 44.6%; alcohol, 24.7%; opium, 10.4%; cannabis, 4.0%; pain-killers, 58.4%; tranquilizers, 0.1%. The sociodemographic characteristics of alcohol and cannabis users were also compared; a comparison of the two groups on psychological tests as well as disability parameters is still being carried out. In the survey, 801 exclusive alcohol users and 127 exclusive cannabis users were found. The combined alcohol and cannabis users numbered only 40. All of them were males. The use of alcohol was more prevalent than that of cannabis in all age groups. Use of both drugs increased with age, but the increase was proportionately greater for cannabis (Table 2). Use of both drugs was most prevalent among Hindus (alcohol, 37.5%; cannabis, 5.8%), intermediate among Jains, a subsect of the Hindus (alcohol, 1%; cannabis, 10.8%), and lowest among Muslims (alcohol, 7.8%; cannabis, 1%). The various caste groups showed significant differences in use patterns. The Brahmins, Sadhus, and Vaish (business community) preferred bhang and ganja. In the so-called martial castes (the Rajputa, Jats, and Gujjars), alcohol was the preferred drug.

Use of alcohol was high in all income groups and highest (36.1%) in the group earning the most money *per capita*. Cannabis use was most common in two highest income groups, i.e., 10.0% in the *per capita* income group of 100–199 Rupees per month, and about 6% in those earning 200 Rupees per month and above, vs only 1.2% in the group earning 60–99 Rupees per month. This finding suggests that perhaps it was no longer the preferred intoxicant of lower income groups. Family structure, total number of individuals in the family, and marital status did not affect the prevalence of drug use. Significant association was observed between the prevalence of alcohol and cannabis use and education. The percentage of cannabis users was highest in the educated group (20.5%) while alcohol was more common in illiterates and the uneducated (38.1%). In the agricultural occupational groups the use rates were 36% for alcohol and 4% for cannabis, while in nonagriculturists, they were 31.6% and 7.7% respectively. When asked about their health status, most subjects assessed their own health as average, but a few chronic alcohol users reported poor health.

The studies on university student populations have yielded widely differing findings. A number of studies in different parts of the country have demonstrated that, as in the general population, cannabis was the second most commonly preferred drug among the students. It was as if a generation was rediscovering the same plant, but now under Western influence. However, the studies with self-administered questionnaires showed very different prevalence rates depending upon the time covered, and the type and structure of questionnaire. Chitnis (1974) reported cannabis ever-use rates of 17%, while Varma *et al.* (1977) found

TABLE 2

Prevalence of Alcohol and Cannabis Use By Different Age Groups in the Rajasthan Survey
(Mohan et al., *1979c)*

	Percentage of Respondents Using During the Past Year	
Age Group (years)	Alcohol	Cannabis
15–19	16.8	1.3
20–29	34.3	4.5
30–39	39.3	7.0
40–49	38.4	5.7
50–59	35.1	5.9

an ever-use prevalence rate of only 2.0%. Mohan and Arora (1976) found a cannabis use one-year prevalence rate of 1.6% among an unrepresentative sample of university students. Sethi and Manchanda (1977) found a one-month period prevalence rate of 14.9% in medical students. Dube (1972) found a prevalence rate of 36.8% among medical students. Singh and Singh (1979) found that among medical undergraduate students the ever-use rate was 28.5% and the current-year (yearly) prevalence rate was 11.0%. Mohan *et al.* (1978b) found a 12-mo prevalence rate of 12% in senior high school students.

Mohan *et al.* (1979b), in a multicentered randomized survey, studied 28,000 urban students spread over the country. The current use rates of cannabis were: Bombay, 0.4%; Madras, 1.5%; Delhi, 1.3%; Jaipur, 0.9%; Hyderabad, 0.7%; and Varanasi, 10.9% (National Committee on Drug Addiction, 1977). In a study of nonmedical and nonstudent youth, Varma *et al.* (1979) found a 30-day period prevalence rate of cannabis use of 52.4%; Mohan *et al.* (1979a), in a similar study on rural nonstudent population, found a prevalence rate of only 0.8%.

Summary of Indian Findings

The studies on cannabis in India fall into three major groups: (i) clinical studies, (ii) studies on long-term effects of cannabis use, and (iii) epidemiological surveys in different population groups. Clinical studies have been of many kinds; they have examined sociodemographic correlates, characteristics of users, motivational factors in cannabis use, and acute and chronic effects. These studies have established the acute adverse effects of cannabis use, which present as toxic psychoses fairly consistently. The clinical studies have not established clearly the occurrence and pictures of mania, dementia, and psychosis. They have also not reported on the occurrence of amotivational syndrome, flashback phenomena, or genetic abnormalities. There have been reports of cannabis psychoses, but these have been inconsistent and unreliable. The only conclusion which can be drawn from these studies is that cannabis use is associated with precipitation of psychiatric illnesses. Studies on long-term effects of cannabis, apart from clinical impressions, have been few.

The clinical data suggest that there are probably no significant nonpsychiatric adverse effects associated with long-term use, other than those which could be attributed to tobacco smoking. Most observations on long-term effects are vitiated by the lack of both controls and careful evaluation of various other parameters such as dose and route of administration. Recently, two studies using controls and careful testing have revealed contradictory results, primarily because the populations tested have been different, i.e., urban and rural. The contradictory results are in line with the observations from Egypt, which have also revealed that the degree of difference between cannabis users and controls varied in rural and urban populations. Hence no definite conclusions in this respect can be drawn.

The epidemiological surveys on different population groups show different trends in urban students and the rural general population. The data from rural population studies show that cannabis use is less than that of alcohol, though the percentage of the population using cannabis is higher than what had been previously estimated in various reports. There is some evidence to suggest a shift in drug use pattern, with alcohol replacing more traditional drugs such as opium and cannabis. This hypothesis is supported by data indicating a steadily rising alcohol production, and also by the observation that cannabis users are relatively more numerous in the middle-aged groups, while more younger people use alcohol. Though alcohol use is by far the commonest in urban student populations, use of cannabis is more prevalent than that of all other drugs. This suggests the possibility that cannabis is being rediscovered by young people, but this trend needs to be confirmed by further longitudinal studies. Summarizing, the major lacunae still existing in cannabis research seem to be in data on the adverse effects of long-term heavy use and in the delineation of cannabis psychosis. In addition to case control studies, epidemiological studies which look at large numbers of cannabis users are needed to answer some of the unanswered questions.

The Philippines

From the Philippines there are three studies available, the first dealing with a survey of college students; the second, a study of street corner use in Metropolitan Manila, and the third covering school populations. The first study (Zarco, 1972a) had the following objectives: (i) to determine the extent of illicit drug use, (ii) to identify the drugs which were used, and (iii) to study factors associated with drug use. An anonymous self-administered questionnaire was used. The respondents were selected by quota sampling technique, 8.4% being taken from each category/class of students. This yielded a sample of 473 out of a total population of 5,631. They found that 29% of the students were using, or had used, marihuana: 23% had experimented with the drug once or twice, 3% smoked once a week, and 3% more frequently. The highest percentages of regular users were found among the freshmen and sophomores, and males used it more commonly than females.

The second study explored the role of certain epidemiological factors relating to drug use in the city of Manila (Zarco, 1972b). The sample was purposive. The survey aimed to study these factors in both upper and lower classes (defined according to the educational status of the father). In addition, it attempted to identify the drugs currently used by these two groups, the sequential development of drug use, the frequency of use, the factors in the spread of drug use, the role of intervention by key persons in the environment (usually family members or peer groups), and to study various other sociodemographic factors. The study was carried out by personal interviews according to a prestructured format.

Significant differences appeared between the wards of parents who had received up to 10 yr of schooling, and those whose parents were graduates of high school, both in terms of frequency of drug intake and the types of drugs used. Individuals who came from higher socioeconomic strata (or affluent groups) tended to initiate drug use in high school. The antecedent use of tobacco and alcohol as points of departure from nonuser to user status was high. For almost 97% of this group, cannabis was the first illicit drug used, although methaqualone was also consumed early. Drug use peaked during the first two years of college. At the time of the survey, the number of drugs self-administered by each subject averaged between six and seven. Opiates and their derivatives were unpopular, but cannabis was in high demand. Some of the drugs were used by this group for specific situational functions, e.g., amphetamine before or during examinations.

The subjects in the criminal justice system, who came from a lower socioeconomic group, demonstrated a pattern of drug use that differed from that of the more affluent individuals in many respects. Although they also consumed tobacco and alcohol prior to initiating illicit drug use during their high school years, only 35% had used cannabis first. Most of the others had tried opiates first and cannabis and other drugs later. In addition, about 50% had first used illicit drugs outside the school environment. Drug use in this group reached a peak earlier (during the senior classes of high school). At the time of the survey, fewer drugs were being used by the prison population (usually three to four), and opiates remained the most popular drugs. When the backgrounds of the subjects were analyzed, it appeared that the majority of prison drug users came from a single district in Greater Manila city, establishing that location as an endemic area of drug use. There was less involvement of girls in the prison group as compared with the affluent group. More than 50% of responders in the two groups had prior awareness of the dangers associated with cannabis use.

To continue and extend the observations of the above two studies, a survey was carried out by Zarco (1975) in which approximately 2,048 students across five cities in the Philippines were surveyed for drug use, by means of a self-administered anonymous questionnaire. In judging the severity of drug problems in any one city as compared to the others, the marihuana ever-use rates were taken as a gross key indicator, since earlier studies had shown this drug to be a "starter drug" among affluent users in the society. The marihuana use rates in the five cities were 21.5, 20.4, 7.8, 7.7, and 6.1%. In general, cannabis use had spread in the country, and its use by the young was very closely allied to the American ethos, including symbolic values and rationalizations.

In the school studies, 51% of the respondents indicated marihuana as the "starter drug" and the correlation between cannabis use and subsequent polydrug use was very high ($r = 0.68$, $p < .001$). Among the major positive correlates of cannabis use were associations with total number of friends taking the drug, schoolmates pushing the drug, awareness of its availability, number of school personnel taking the drug, teachers' encouragement of drug use, number of family members taking drugs, parents' drinking frequency, father's smoking, and parental educational levels. All were significant at the $p < .005$ level. These correlates reflected the extremely social nature of cannabis use, especially in children of those parents who had had a Westernized education and were influenced by it.

The cannabis user profile that emerged was as follows: men had greater involvement than women; the age of starting was as early as 13 yr, but the peak age was 16-18 yr for both men and women. Use fell with rise in age of respondents. The third and fourth year high school students used cannabis most, followed by first and second year college students and third and fourth year college students. There was an inverse relationship between grades in examinations and cannabis use. The communication between parents and the drug user was impaired, though paradoxically the use was slightly more in those who lived with their parents than in those who did not.

On critical evaluation of the study it was apparent that the estimates were valid for minimum use rates and did not give true rates of marihuana use. The study was conducted in the latter part of the year, by which time under-achievers would have dropped out due to academic pressure, thus permitting a false correlation in the grades vs drug use as observed. The authors conclude that reliability of results was good, as the proportion of respondents using drugs in the main surveys corresponded closely with pretest results. This method of validation is open to criticism.

5. LACUNAE IN DEVELOPING COUNTRIES

In relation to future needs and gaps in present knowledge, it is obvious that in order to look for any significant contributions to our understanding of cannabis abuse, large-scale field studies are needed to locate long-term users in their natural surroundings. It is necessary to devise tests which are culture-free, situation-specific, and replicable, keeping in account the age, education, dose, duration of use, and rural/urban differences. Some of the phenomena associated with long-term use, such as flashbacks, the amotivational syndrome, cerebral atrophy, cannabis psychoses, and genetic deficits may be so rare that a study involving large numbers of users would be necessary to observe them. It is obvious that case control studies have contributed as much as they can, and now have to be supported by longitudinal studies to clarify unanswered questions about the adverse sequelae of long-term use. These studies could also incorporate in an elective way the beneficial aspects of cannabis use and its therapeutic potentials. Effective links between the international agencies such as the WHO or UNICEF and developing and developed countries are necessary. In relation to cannabis, some of the developing countries still constitute natural field laboratories where effects of long-term cannabis use can be studied by utilizing epidemiological methods to focus on the adverse effects.

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The Epidemiology of Cannabis Use and Its Health Consequences in Western Countries

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1. INTRODUCTION

The current vogue of cannabis is one of the most completely chronicled of all recent drug fads. Virtually from the first beginnings of its spread of popularity in the 1960s, researchers have studied cannabis use among a variety of student and adult populations in North America and elsewhere. Although cannabis has a long history in some countries, its use in North America and Europe is fairly recent. The drug was brought from North Africa to France about 1800, but the first recorded ingestion there seems to have been about 1850. Its regular use in North America was first noticed in the 1920s. At that time, however, cannabis smokers seemed to be mostly musicians, slum dwellers, and minor criminals, rather than the respectable middle classes or young people. Currently, cannabis smoking is very common in most youthful North American populations. Indeed, it seems to be normative in at least some groups, i.e., nonusers are in the minority. Since cannabis consumption is increasing, it appears likely that the adverse consequences associated with its use will also increase.

It would be impossible in the space of this review to summarize and interpret all of the available studies of cannabis use and its adverse consequences in humans. For Western countries alone they number in the hundreds and many are simply observations of the frequency of use in selected populations. Some reports are also not available in the open scientific literature or have appeared in languages other than English. This review includes studies from Europe and North America, that is, countries where cannabis use is relatively recent and not sanctioned by long tradition. The aims of this review are to:

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(i) describe the frequency of use and heavy use in both general and special populations, in order to define the size of the total population at risk for adverse reactions;

(ii) identify trends in cannabis consumption over time;

(iii) determine the factors associated with use, especially heavy use, in order to establish clearly the characteristics of those most at risk for adverse reactions;

(iv) determine the incidence and severity of adverse reactions in human populations and the factors associated with them; and

(v) indicate the need for further research, especially research on the prevalence of health consequences of use and the identification of those most likely to suffer such consequences.

The review is limited to human studies of an epidemiological, experimental, and clinical nature.

2. EXTENT OF CANNABIS USE IN GENERAL POPULATIONS

There appears to be no recent review of this subject which takes an international perspective. Several recently available reviews, for example those by Jessor (1979) and Kandel (1980), include data only from the United States and to a limited extent from Canada. The review of Mercer and Smart (1974), which analyzed drug-use studies on a worldwide basis, is now considerably out-of-date. For the purposes of the present paper, epidemiological data were sought for all Western countries for the years 1974 to 1980. Reports from 10 countries (Australia, Belgium, Canada, Denmark, Mexico, Netherlands, Norway, Poland, United Kingdom, and the U.S.A.) were located and the major findings have been summarized in Table 1. As expected, the largest volume of literature on cannabis comes from the United States, Canada, and the United Kingdom. In this paper, however, these countries are represented by only three studies each; the largest and most recent have been included while many others have been left out.

It can be seen from Table 1 that precise comparisons are difficult to make. Different samples (households, students) and differing age groups were investigated in a variety of years. Nevertheless, it appears that in Canada and Australia about 17% of the adult general population have used cannabis, but only about 4.0% use it daily. In the United States, about 19% of the general population above the age of 12 had used cannabis, but the prevalence of daily use is not known. In Canada and Australia daily users among adults comprise about a quarter of those who have ever used cannabis and about 40%–50% of those who have used it in the past 12 mo.

Rates of "ever" use[1] among high school and college students in Canada, Australia, Norway, and the United Kingdom are roughly similar (23.0% to 31.7%) and much lower than those in the U.S.A. (more than 60% ever used). Daily or "regular" users comprise about 4.0% of the student population in Australia, 3.0% in Denmark, 0.16% in Belgium, but 10.3% in the U.S.A., and 11.7% in Poland. The prevalence of daily use is apparently not known for student populations in Canada, United Kingdom, Mexico, the Netherlands, Norway, or the countries not surveyed. These data strongly suggest that both use and heavy use of cannabis are greatest in the U.S.A. and that adverse reactions should be reported more often from that country than from European or other North American countries.

3. EXTENT OF CANNABIS USE IN SPECIAL SAMPLES

In general, studies of rates of cannabis use in general adult populations are far fewer than those in special populations identified as most likely to use cannabis. The most frequently studied group is high school students, followed by specially identified occupational and other groups with high likelihood of use, especially school drop-outs, soldiers, and patients in social and psychiatric services.

Drop-outs and Absentees

Two groups of investigators have studied students who were absentees from school. Haberman *et al.* (1971) contacted those who were absent from school on the day of a drug use survey and these students were found to be heavier users of all drugs than the students at school on that day. Kandel (1975a) interviewed, in their houses, students who had been absent on the day of a school drug survey but this group did not report more drug use than nonabsentees. A second sample contacted by mail and asked to come to a survey center for a group administration of the questionnaire did report more drug use than regular students. Unfortunately, very few students who were contacted by mail actually participated in the second study.

Rates of cannabis use among early school drop-outs have been

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[1] The "ever" use category includes all subjects who have used cannabis at least once.

TABLE 1

Surveys of Rates of Cannabis Use in Various Countries

Country	Type of Sample	Ever Used Male %	Ever Used Total %	Ever Used Female %	Past 12 Months Male %	Past 12 Months Total %	Past 12 Months Female %	Daily Users Male %	Daily Users Total %	Daily Users Female %	Factors Associated with Use	Reference
Australia	Household (13–60 yr)	23.0	17.0	11.0	15.0	12.0	7.0	9.0	6.0	4.0	—Sex (twice as many males as females report use) —Age (most common for 18–24-yr-old group)	Heine and Mant, 1979
Australia	Students (year 10)					26.9 (Current use)			2.2 (Most days)		—Sex (males using more) —Friends' use (positively related)	Champion *et al.*, 1978
Belgium	Students (12–24 yr)					0.04			.016			Decrucq and Sand, 1973
Canada	Students (grades 7, 9, 11, and 13)				36.4	31.7	26.8				—Performance average (negatively related) —Age (highest among 16–17 yr olds) —Performance average (highest among grade 11s)	Smart *et al.*, 1979

Canada	Adults (household survey of ⩾18-yr-olds)	20.2	17.2	13.8	12.2	9.7	7.2	5.0	3.6 (>once per week in past 30 days)	1.9	—Young, urban, male laborers, persons with high school or university education, and those whose mother tongue was English were most common users	Rootman, 1979
Canada	Household				8.2	5.8	2.3				—Young, urban males with high school or university education, especially those with high incomes, in professional or executive positions, and who speak English as a first language are most common users.	Smart and Goodstadt, 1976
Denmark	Students (universities and institutes of higher education)		37.0						3.0 (Regularly)		—Friends' use (positively related) —Use more common among students who are less conforming, have a less smooth course of study, and have family problems (psychic or alcoholic trouble)	Ulff-Møller, 1971
Mexico	Students (14–18 yr)					1.6						Castro *et al.*, 1979
Netherlands	12–18-yr-olds		3.0			1.0 (Current use)						van der Wal, 1978

TABLE 1 (CONTINUED)

Country	Type of Sample	Ever Used			Past 12 Months			Daily Users			Factors Associated with Use	Reference
		Male %	Total %	Female %	Male %	Total %	Female %	Male %	Total %	Female %		
Norway	15–21-yr-olds		22.5								—Use of other drugs (positively related) —Most intense use by 17–18-yr-olds	Irgens-Jensen and Rud, 1979
Poland	Students								11.7 (Regularly or commonly abused)			Marek and Redo, 1978
United Kingdom	Students (university)		29.0			14.7 (Current use)					—Tobacco smoking (positively related) —Alcohol use (positively related)	Einstein *et al.*, 1975
United Kingdom	Students (university)					32.0					—Age (within 1st yr students positively related) —Favorable attitude toward cannabis use —Religion (current affiliation and frequency of attendance are both negatively related) —Alcohol use (positively related)	Kosviner *et al.*, 1974

U.S.A.	Students (high school seniors)	65.0	60.4	55.7	55.8	50.8	45.7	12.7	10.3	7.3	—Older males —Those not intending to go to college —Attitude toward use (positively related)	Johnston *et al.*, 1979a and b
									(30 day prevalence of daily use)			
U.S.A.	Students (grades 7–12)	65.2		62.8	46.7		41.9	31.2		24.6	—Grade (positively related) —Sex (males using more)	Blackford, 1977
						(used ⩾ 10 in past year)			(used ⩾ 50 in past year)			
U.S.A.	Nationwide household survey										—Age (people aged 18–25 form highest use cohort) —Sex (use more common among males)	Abelson and Atkinson, 1975
	1.adults (⩾ 18 yr)	24.0	19.0	14.0	13.0	10.0	8.0					
	2.youth (12–17 yr)	24.0	23.0	21.0	19.0	19.0	18.0				—Race (use more common among nonwhites) —Education (use more common among those with some college education)	

examined in several studies. Winburn and Hays (1974) administered a drug use questionnaire to adolescents who had left school and entered a federal remedial education program. Comparisons were made with data obtained from students in the same area. Drop-outs used all drugs (marihuana, barbiturates, stimulants, solvents, etc.), except alcohol and opiates, more frequently than students. Drug use in the drop-out group was more common among males than females, among those who dropped out early rather than late in their school careers, and among whites than among blacks and Mexican-Americans.

More direct evidence of how school drop-out status affects drug use is found in the study by Annis and Watson (1975). Their report is one of the few which have provided information on drug use both before and after dropping out from school. They administered a drug use questionnaire to 915 students in the first year of high school (the total sample available) and one year later to 88 members of the original group who had meanwhile dropped out. More drop-outs, as expected, used drugs (cannabis, tobacco, alcohol, speed, barbiturates, hallucinogens) than those who had remained in school. For almost every drug "the trend towards greater drug use within the drop-out group was evident and equally strong before the drop-out occurred."

Carlin and Post (1974) rather indirectly explored the relationship between drop-out status and drug use. They interviewed 266 volunteers who were contacted through advertisements in a university newspaper. As expected, a much larger proportion of school drop-outs than of graduates reported using cannabis and hallucinogens. Those who were unemployed reported more use than those who were currently working or in school.

A study by Mellinger *et al.* (1976) of male university students has explored the real connection between cannabis use and dropping out. They found that cannabis users did not drop out more frequently than would have been predicted on the basis of their background characteristics and academic motivation. Multiple drug users did drop out more frequently than nonusers. Moderate or light cannabis use was not associated with high drop-out rates.

The drop-out studies are consistent in showing that students who leave school early are more likely to use cannabis than those who do not. However, the initiation of cannabis use seems sometimes to precede and sometimes to follow dropping out of school. Also, multiple drug use and background characteristics may be just as important as cannabis use in causing early drop-out. Because early dropouts are likely to be heavier cannabis users, it is likely that surveys of students actually in school underestimate the rates of use and of adverse reactions in young populations.

Studies of Special Occupational Groups

A few scattered investigations have been made of occupational groups typically composed of young people. The groups studied most often are those in the military services, especially American soldiers who went to Vietnam or West Germany. Surprisingly, the study of people most vulnerable to drug use has not typically focused on those most closely associated with it in their work or those who handle illicit drugs. One might expect to find systematic studies done among farmers who grow cannabis plants, or customs and airline personnel, policemen on drug squads, and the like. However, none is available on these groups.

The prevalence of cannabis use and of adverse reactions has been studied most extensively in American soldiers—especially those who went to Vietnam. These army surveys are typically based on excellent sampling methods and large numbers of subjects. Of course, military institutions typically keep good records and can insist upon compliance, whether it be with life history interviews, questionnaires, or urinalyses. Stanton *et al.* (1976) have summarized most of these studies in a recent review. Tennant *et al.* (1972) found that of 3,553 American soldiers stationed in West Germany, 46% had used illegal drugs at least once and 16% more than three times per week. Hashish was the most commonly used drug. Stanton *et al.* (1976) found about the same rate of use in soldiers in Vietnam. In general, the results show a high level of cannabis use in military populations although comparisons with civilian populations of comparable age, sex, race, socioeconomic status, etc., are often not made.

A novel study was conducted by Nelson *et al.* (1974) concerning drug use among "Job Corps" members in the U.S.A. The "Job Corps" members are typically young people (age 16–21) from poor backgrounds and ethnic minority groups. Often they come from areas in which drug availability is high and where there are many addicts. The authors surveyed 1,357 enrollees and 440 staff from 19 training centers in 17 states. Surprisingly, neither past nor current drug use was found to be high; 90% were not using any drug except alcohol, tobacco, or marihuana. Only 31% reported having used marihuana. These figures are lower than would be expected in comparable populations and the results are difficult to explain.

Several efforts have been made to study the rate of cannabis use among persons charged with or convicted of crimes not related to drug use. Many illicit drugs are costly and users in certain settings support their habits by theft, prostitution, or other illegal activities. Also, the purchase of drugs may force young users to associate for the first time in their lives with persons having criminal connections. Those who elect to do so may have engaged in delinquent or criminal behavior themselves and hence find the transition an easy one. All these possibilities suggest that young persons charged with delinquency or adult criminal offenses would be more extensive users of illicit drugs than those not charged.

Fish *et al.* (1974) studied drug use among five groups in Glasgow. Three groups—venereal disease patients, casualty patients, and young offenders—had higher rates of drug use than did a variety of student groups. The young offender group comprised 321 males aged 16–20 years, randomly drawn from two correctional institutions. As expected, the young offenders were much heavier drug users than the members of any other group. About 57% had used illicit drugs and 18% used them regularly. Of the occasional and regular users, 69% had used cannabis; 53%, pep pills; and 36%, LSD.

One of the largest studies of juvenile offenders in relation to drug abuse was reported by Stenmark *et al.* (1974). They evaluated 268 consecutive dispositions in juvenile courts in most of a southern state in the U.S.A. Among the young offenders, there was a close relation among the use of alcohol, marihuana, and other drugs, but the proportions using the various drugs are not shown. Juvenile drug use was also positively correlated with parental alcohol use.

In general, it seems likely that criminal, i.e., police- and court-identified, samples of young persons will contain large proportions of heavy drug users and frequent cannabis users. However, the methodology and the sampling procedures used in these studies leave much to be improved. The background reasons for the high rate of drug use have also not been explored.

High proportions of nonmedical drug users (including cannabis users) have sometimes been found in groups of adolescent patients being treated in psychiatric or medical services established specifically for young persons. For example, Rosenberg and Dolinsky (1972) studied 100 persons aged 15 to 25 attending an acute psychiatric service at an American general hospital. Unfortunately the sample was not random. The selection of subjects depended upon when the authors were available for interviews. At least 17 subjects were drug-dependent (chiefly on heroin, barbiturates, and amphetamines), and 58 of the 100 had used illicit drugs (including cannabis) on at least six occasions. Also, 12 were judged to be pre-alcoholics and five were alcoholics. Heavy drug use was related to dropping out of school, work difficulties, delinquency and a psychiatric diagnosis of personality disorder.

Chall (1973) interviewed 523 patients at an adolescent medical service in an American general hospital. The sample consisted of consecutive first admissions to a service intended primarily for low income young people. About 19% were using heroin, 9% barbiturates, 7% stimulants, and 7% LSD. About 8% used cannabis; only 4% mentioned using hashish and none was using it regularly. For most drugs these rates are probably not much greater than in a comparable general population, but for heroin it is almost certainly higher. Of the 40 adolescents interviewed in depth, 17 had used heroin and 5 had been addicted.

Jackson (1973) reported on 31 adolescents referred to a children's diagnostic center attached to welfare and family court agencies in Colorado. All were referred for drug abuse but they represented only 4% of the total referrals. Other anomalies were that the "drug abusers" group contained nearly equal numbers of males and females, and there were no blacks among them although there were many in the total population. These findings suggest that the area served by the center may be unusual or that the drug abusers were often missed in the identification process.

In summary, it appears that sometimes populations of medical and psychiatric patients contain large proportions of cannabis users and sometimes they do not. At present, the reasons for the variations are difficult to establish. Data from child welfare agencies are difficult to interpret and the results may vary depending largely on the area served by the agency and the methods of identification.

4. TRENDS IN CANNABIS USE OVER TIME

Even casual observers will agree that cannabis use has increased greatly in developed countries over the past 15 to 20 years. However, only a few countries—Canada, U.S.A., Australia, and Norway—seem to have actual trend studies available (see Table 2) in which the same questionnaire and the same sampling design have been employed on several occasions. All four countries showed remarkable increases in rates of cannabis use from the late 1960s to the late 1970s. For example, only 6.7% of students in Canada in 1968 but 31.7% in 1979 used cannabis (Smart *et al.*, 1979). Annual household surveys in the U.S.A. (Abelson *et al.*, 1977) showed that the percentage of young people (aged 12 to 17) who smoked cannabis increased from 15% in 1971 to 22% in 1977.

TABLE 2

Studies of Time Trends in Cannabis Use

Country	Type of Sample	Cannabis Measures	Year	Prevalence Whole Sample	 Males	 Females	Major Demographic Variables Associated with Cannabis Use	Reference
Canada (i)	Students in grades 7,9,11,13; n = 3,479 to 8,865	% used in past 6 mo	1968 = 1974 =	6.7% 22.9%	8.6% 25.5%	4.1% 20.3%	Age (continuing increase of use with age), sex (differences declining)	Smart and Fejer, 1975
Canada (ii)	Students in grades 7,9,11,13; n = 4,700	% using in past year	1977 = 1979 =	25.1% 31.7%	29.4% 36.4%	21.1% 26.8%	Age (continuing increase of use with age), sex (differences declining)	Smart *et al.*, 1979
Australia	Students in grade 10; n = 504	% current use	1971 = 1977 =	6.5% 26.9%			Sex (males continued using and using more often, but difference between sexes declining), friends' use (use increases with number of friends who use)	Champion *et al.*, 1978
Norway	15–21-yr-olds; n = 729 to 1,027	% ever used	1968 = 1972 = 1979 =	5.3% 18.8% 22.5%			Use of other drugs (positive relationship)	Irgens-Jensen and Rud, 1977, 1979

U.S.A. (i)	High School students; n = 15,791 to 18,924	% used in last 12 mo	1975	=	40.0%	45.8%	34.9%	Geographic regions (differences declining), sex (older male students most common users), education (greater use by those not intending to go to college), attitude toward use (positively related to use)	Johnston *et al.*, 1979a and b
			1979	=	50.8%	55.8%	45.7%		
U.S.A. (ii)	Students in grades 7–12	% use in last year (grade 11 only)	1968	=		36.9%	31.7%	Grade (continued increasing trend with grade level), sex (males continuing to use more but high rates of increase for females)	Blackford, 1977
			1977	=		65.2%			

Among adults, fewer than 1% of the general population had smoked cannabis in the U.S.A. and Canada in the late 1960s. By the late 1970s the proportion had risen to 17.2% in Canada (Rootman, 1979) and 25% in the U.S.A. (Abelson *et al.*, 1977). Comparable increases seem to have occurred in youthful populations in Australia and Norway, but not in Mexico (Castro *et al.*, 1979).

Currently there are some signs of stabilization in rates of use. The latest studies of high school seniors by Johnston *et al.* (1979a and b, 1980) showed no increase in 1980 and 1979 over 1978, and a higher than usual proportion reporting that they viewed cannabis as having harmful effects. Also, there has been no increase in youthful use in Mexico and a recent decline in the rate of increase in Norway (Irgens-Jensen and Rud, 1979). Rates of cannabis use continued to increase among Canadian youth until 1979 (Smart *et al.*, 1979) where increases in both sexes and at most ages were observed. The most recent figures (Smart *et al.*, 1981) suggest that stabilization may be occurring in that country as well.

Apparently there are no investigations of changes over time in the extent of use by school drop-outs, or by special occupational or other groups likely to consume cannabis. There are also no longitudinal studies showing how use changes as people move from the teenage years into adulthood and middle age. Limited information derived from the "Monitoring the Future" study suggests that the most frequent users are likely to maintain their marihuana consumption for at least five years after graduation from high school (Johnston, 1981).

5. FACTORS ASSOCIATED WITH USE

Cannabis, like all drugs yet studied, is heavily used by some segments of the population and hardly at all by others. Of course, the heaviest and most frequent smokers should be those most at risk for developing adverse effects. Certain demographic characteristics such as age, sex, and socioeconomic status, along with previous alcohol and drug use and psychological problems, seem to be the best predictors of use.

Age

Few drugs show such age-specific rates of use as does cannabis. Most studies indicate that cannabis consumption before age 13 is unusual; for example, Smart *et al.* (1981) found that only 5.7% of students 13 and under had used cannabis within the previous year, compared to 25.3% of those 14–15, 45.5% aged 16–17, and 37.1% aged 18 and over. The ages 15 to 17 are the years when cannabis is typically first smoked (Miller *et al.*, 1978). Currently in the U.S.A. there are about twice as many daily users of cannabis as of alcohol among high school seniors (Johnston *et al.*, 1979b). Among older male high school students in both Canada and the U.S.A., it is unusual not to have tried cannabis, although heavy (daily or weekly) use is still unusual.

Rootman's (1979) studies of adult populations and those of Abelson *et al.* (1977) showed that use is most common among those 18–25 yr old (39.8% in Canada and 60% in the U.S.A. respectively). Use is insignificant in those over 50 (2.4% in Rootman's study) and almost nonexistent in those over 70. As Kandel (1980) has pointed out, these age-related trends are very different from those for stimulants, tranquilizers, alcohol, and tobacco.

Currently, cannabis use is strongly age-related but we cannot be certain whether this will continue. As the 18 to 25 age cohort grows into middle age, it is possible that they will decrease their consumption of cannabis, but there is no longitudinal study to demonstrate this empirically.

Sex

Virtually all available studies show a clear sex difference in the use of cannabis, as of most illicit drugs (see Table 1). The ratio of males to females seems to vary somewhat from one country to another, but with males always higher. Surveys in Canada show a male:female ratio of 2:1.4 for ever use but 5:2 for heavy use (Rootman, 1979). In Australia, the respective ratios are 2.1:1 and 9:4. However, in the U.S.A., males and females are more similar in their rates of cannabis use. For example, Johnston *et al.* (1979a and b) found male and female high school seniors to be close in rates of "ever" use (65.0% vs 55.7%) but rates of daily use for females were less than 60% of those for males (Blackford, 1977; Johnston *et al.*, 1979a and b). Much of the current increase in overall rates of use is accounted for by females (Abelson *et al.*, 1977; Smart *et al.*, 1979).

Given the sex differential in rates of heavy use, it can be predicted that adverse consequences would occur about twice as often in males as in females in Canada and slightly less than that in the U.S.A. The ratio of males to females suffering adverse effects should be higher in other countries.

Socioeconomic Status

Rates of cannabis use have shown an inconsistent relationship to socioeconomic status. Some studies found no relationship (e.g., Kandel *et al.*, 1976; Jessor, 1979) but others have. Rootman (1979) found the highest rates of use among laborers in his study of adults, but among students, Smart *et al.* (1979) found higher rates in those whose fathers were professionals.

Other Drug Use

The association of cannabis use with that of alcohol and other drugs is well-established. Numerous studies (Smart and Fejer, 1973; Goode, 1974; Kandel, 1975b; Johnston *et al.*, 1979a and b) have shown that cannabis users are more frequent consumers of all other drugs (including alcohol and tobacco) than are nonusers. This seems to be the case for both adults and young persons. The more frequent the cannabis use the greater the probability that other drugs are also employed. Kandel (1975b) has found that use of alcohol and tobacco typically precedes that of cannabis and, without prior experience with them, experimentation with cannabis is unlikely. However, the available data clearly show that cannabis does not substitute for other drugs used for nonmedical purposes. Moreover, in large populations, trends in cannabis use frequently follow a pattern different from that of other drugs. For example, in the two largest youth samples studied in Canada and the U.S.A. (Smart *et al.*, 1979; Johnston *et al.*, 1979a and b), cannabis use still increased when that of most other illicit drugs did not.

A recent study by Smart and Liban (1980) has shown that cannabis use and self-reported alcohol problems[1] are related, among both adults and students. Multivariate analyses of two large samples showed that age and alcohol problems were the best predictors of cannabis use.

All of these studies suggest that the heaviest users of cannabis, i.e., those at greatest risk for adverse reactions from cannabis use, tend to be users of many other drugs. Separating the effects of cannabis from those of other drugs is therefore difficult when clinical cases of adverse reactions are presented.

Miscellaneous Social Factors Associated with Cannabis Use

A variety of sociodemographic factors have been regularly found to be related to cannabis use. Among them are poor school performance, having friends who were users, having parents who were heavy drinkers and drug users, and involvement in delinquency and minor deviance (Jessor, 1979; Kandel, 1980). Since most such variables do not relate closely to adverse consequences for health, they are not of crucial interest to this review.

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[1] As assessed by the Williams Scale of problem drinking and frequency of alcohol use.

Cannabis, Personality, and Psychological Problems

A detailed discussion of the vast literature on cannabis and personality variables is beyond the scope of this paper, since such variables have not been implicated in adverse health reactions. This literature has been well reviewed by Jessor (1979). In general, there is strong evidence that cannabis use is related to:

(i) Nonconventionality—users are somewhat dissatisfied with society, critical of its norms, and often feel alienated from it;

(ii) Openness—users are more open to experience, uncertainty, and novelty, and are prone to sensation-seeking;

(iii) Achievement—users tend to value conventional achievement less and have fewer expectations of being successful; to some extent their cannabis use can be seen as a response to frustration.

Just how such variables would relate to the true or reported freqency of adverse reactions is very difficult to surmise and no one seems to have attempted it yet.

Another aspect of personality, more important for the interpretation of adverse health consequences, is that of psychological problems. Again, the data are inconsistent. Several investigators in the U.S.A. (Cross and Davis, 1972; McAree *et al.*, 1972; Stokes, 1974) have found no association between cannabis and psychological problems in general populations and students, except among heavy users (Cross and Davis, 1972). However, Linn (1972) did find an association, among American college students, between cannabis use in general and symptoms suggestive of psychopatholgy. In addition, Smart and Fejer (1973) in Canada and Wells and Stacey (1976) in Scotland found that cannabis users did have more psychopathology than nonusers. It may be that in many groups in the U.S.A., occasional or exploratory use of cannabis is normative and therefore unlikely to be linked to psychopathology. In Canada and Scotland, rates of use are much lower and at the time these studies were done cannabis smoking was certainly not normative. In circumstances where there is little social support for using cannabis, those with psychological problems may be more attracted to it. The evidence for the alternative explanation, i.e., that heavy consumption of cannabis causes or exacerbates such problems, is considered elsewhere in this volume.

It should also be noted that the Greek study of heavy hashish users by Stefanis *et al.* (1976) also found a greater incidence of psychiatric disorders among users (38.0%) than controls (17.5%). The differences were due mainly to a greater prevalence of personality disorders of the antisocial type among users. The degree of psychiatric disturbance was not related to the amount of cannabis consumption.

Summary of Extent of Use and Correlated Factors

The studies reviewed above indicate that the extent of cannabis use varies from one Western country to another, with the highest rates of use (and daily use) in the U.S.A. Rates have been increasing rapidly, especially among women and younger persons, although there are limited signs of a leveling off. Consumers of cannabis are more often male, under 25, and users of other drugs, and (in some groups) they have more signs of psychopathology.

6. EXTENT OF ADVERSE REACTIONS TO CANNABIS

Knowledge about the frequency of various adverse reactions to cannabis is difficult to assemble. There can be no doubt that adverse reactions related to cardiovascular functioning, dependence, sexual and hormonal abnormalities, and psychological disturbances occur *at some times and in some users.* However, the epidemiologist would like to know how often they occur, in what types of users, and to identify the explanatory variables in terms of amount of cannabis exposure, the previous use of other drugs, and psychosocial characteristics. The epidemiologist would also like to know whether or not there is a "safe" dose of cannabis, at or below which users are not at risk for adverse consequences.

Answers (such as they are) to these questions typically come from studies not ideally designed to answer them. As Halikas (1974) pointed out a few years ago, the ideal method for studying the relation between cannabis and psychiatric problems would be to collect a representative sample of cannabis users, have them interviewed and tested by observers without prior knowledge of their drug habits, and compare them with a matched control group of nonusers. Of course this would be a good method for investigating all types of adverse reactions, not just those of a psychiatric nature. Studies of this type have apparently not been done yet for any adverse reactions.

Usually, we must depend upon studies done in several ways:

(i) Anonymous self-report surveys (usually of students) which attempt to gather information about the frequency of use and of certain types of adverse reactions, usually psychological, since physiological changes (e.g., hormonal, cardiovascular, or neurological) will not be known to the users themselves. Unfortunately, we rarely know the dose accurately in such studies, although we may ascertain the frequency of use.

(ii) Experimental studies in which information is gathered about biochemical and other changes after known doses of cannabis. Such research almost always involves only volunteers who are occasional or even regular users. Interpretation of these studies may be confounded by special problems associated with regular use (e.g., development of tolerance).

(iii) Clinical investigations of people seeking treatment for some problem connected with cannabis use. Again the dose is usually uncertain and the investigator must depend greatly on the patient's recall for information related to the drug experience.

All of these approaches have limited ability to answer the types of question asked by the epidemiologist, such as "How common are adverse reactions to cannabis?" and "Which users are at highest risk?" Nevertheless they are the material with which we must work, and they merit examination with these questions in mind.

Surveys of the Extent of Adverse Reactions

Numerous studies have been made of adverse psychological consequences in specially selected large populations. Halikas *et al.* (1971) asked about both pleasant and unpleasant reactions experienced by 100 regular cannabis smokers (who had used the drug at least 50 times). A majority of the respondents reported that the "usual" effects were pleasant (e.g., calmness, restful sleep, clear mind). However, 16% reported the usual occurrence of unpleasant effects, e.g., anxiety, hallucinations, depression, and aggression. Tart (1970) also found that 80% of a sample of "regular" users reported paranoid and suspicious feelings occurring at least once within the previous six months as a result of cannabis use.

Stanton and Bardoni (1972) found that 1.3% of enlisted men in the U.S. Army reported "flashbacks" to their cannabis experiences. Further analysis of the same data (Stanton *et al.*, 1976) showed that of 31 "habitual" smokers (200 or more times) who did not use LSD one reported a flashback, and three of 348 nonhabitual smokers did so. The authors concluded that the data do not support the hypothesis that cannabis-induced flashbacks require a history of heavy use.

Annis and Smart (1973) reported on data from two samples of students, one in a large metropolitan area (n = 6,641) and one in a smaller area (n = 3,304). In the first sample, 19.1% reported experiencing confusion, anxiety, or other unpleasant effects during acute intoxication on at least one occasion, 5.7% more than twice and 1.9% more than seven times. In the second sample, the comparable figures were much higher (37.3%; 10.0%; and 4.0%, respectively) but there is no obvious explanation for the difference. In the first sample, unpleasant recurrences ("flashbacks") were reported as occurring at least once by 14.8% and two or more times by 5.0%. In the second sample the figures were 28.3% and 10.3% respectively. Recurrences were slightly more common among students who had used LSD and other hallucinogens than among those who had used only cannabis. Clearly, Annis and Smart (1973) found a rather high level of unpleasant reactions to cannabis in a population consisting mostly of infrequent users. Variations from one sample to another can be expected, and use of other drugs increases the reported rate of recurrences and adverse reactions. The study also indicates that unpleasant reactions do not disappear after further experience with cannabis, since very frequent users also reported them.

Negrete (1974) reported a similar study but based on a smaller sample. He asked 292 students who had not regularly used any hallucinogenic drug (other than cannabis) at an English-speaking university in Quebec to report on various adverse reactions that they had experienced at least once. Flashbacks were experienced by 61% and were more common among women. Prolonged intoxication (31% of users), paranoia (44%), mistrust (30%), panic and sense of imminent death (9%) also occurred. These adverse reactions seemed to occur less frequently in heavier users.

Several studies have been made of the incidence of psychological adverse reactions among large samples of heavy users. Tennant and Groesbeck (1972) reported on 720 hashish users referred or self-referred for medical or psychiatric reasons or for information about drugs. About 55% were defined as "experimental or occasional" users (10–12 g monthly) and 15% were very heavy users (50–600 g monthly). Flashbacks were not seen in any users who did not also take hallucinogens. No adverse effects other than minor respiratory ailments were seen in soldiers using less than 12 g hashish per month. The most common adverse reactions were chronic intoxication, schizophrenic reactions, and acute toxic reactions. Most of the acute toxic and schizophrenic reactions (80%) were caused by multiple drug use.

Naditch *et al.* (1975) examined 483 drug users obtained by means of a "chain of referral" sampling method. They found that neither the psychological set and the setting of cannabis use nor the extent of use were predictors of adverse reactions. However, the degree of maladjustment, regression, and schizophrenia as measured by selected scales of psychopathology were good predictors.

Weller and Halikas (1980) give some indication of how common serious adverse reactions and problems are among heavy users. They studied 97 heavy cannabis users who had been identified five years earlier. At the time of the follow-up, only 10% were diagnosed as "abusers" in terms of having adverse psychological and physical consequences, control problems, social and psychological problems related to cannabis, and "adverse opinions" (i.e., the belief by the user himself, or by others, that he uses too much cannabis). However, only 44% of users were totally free of symptoms related to the above.

Questionnaire-based studies provide interesting but limited information about adverse reactions. They can give information only about subjective effects and not about the vast number of biochemical and physiological consequences that can be seen with sophisticated bioassays and tests. Also, such questionnaires typically enquire about experiences close to normal behavior, e.g., depression, mistrust, and anxiety, that seem only indirectly related to the serious panic, anxiety, or psychotic reactions described in clinical studies. Individuals who have had these more serious reactions to cannabis would be less likely to remain in school and hence would probably not be included in studies of student populations. No studies seem to have been conducted on general populations to determine the incidence of adverse reactions serious enough to require treatment or hospitalization. Indeed, no studies have been made of the incidence of adverse reactions in general *adult* populations of cannabis users, whether of a serious or nonserious nature.

Experimental and Biochemical Studies

Much research has been conducted on the effects of graded doses of cannabis on different biochemical and neurological functions (see Miller, 1974, for a review). Usually very little information on the frequency of adverse reactions in large populations of users can be expected from such investigations, since they were not designed specifically for this purpose. However, they could give an accurate indication of such frequency if the subjects were selected randomly from the population of cannabis users. Typically, however, most investigators have examined a narrow range of the cannabis-using population. For example, virtually all studies of tolerance and dependence and cardiovascular changes have been conducted on young males. Only Stefanis *et al.* (1976) in their study of chronic users in Greece used some older males.[1] Most subjects have had previous experience with cannabis and many are regular cannabis users. The same is true of studies of sexual and hormonal changes. In addition, the sample sizes are usually small, ranging from 1 to 50 in most instances. Hence the chances of detecting uncommon forms of adverse consequences could be quite small. Few of the experimental studies in which adverse consequences have been found (e.g., cardiovascular, neurological, hormonal) have yielded information on the types of users in whom they are most likely to occur; hence high risk individuals cannot be identified.

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[1] It is recognized that in many countries drugs cannot be given experimentally to females of child-bearing age and hence, males are the only choice.

Clinical Studies

Much of our knowledge of the adverse psychological consequences of cannabis use comes from studies of clinical populations—persons presenting in hospitals, clinics, counseling centers, and the like, with one or more problems related to cannabis use. The value of such studies is that they can investigate serious adverse phenomena associated with cannabis use as it occurs in the "real world" rather than under controlled conditions. Unlike survey studies, they are concerned with symptoms serious enough to require treatment and, unlike many experimental studies, they generally involve levels of exposure to cannabis (and to other drugs) which can be accepted as heavy and frequent. Clinical observations and case history material can be collected in depth and supplemented by laboratory investigations. Unfortunately such studies do not permit easy inferences about the frequency of adverse reactions due to cannabis. It has been shown earlier that many cannabis users are users of other drugs and that some users and many heavy users have preexisting psychological problems.

Given this difficulty, what can we conclude from such studies about the general epidemiology of adverse reaction? If we accept that all inferences are tentative, at least a few can be suggested. Most of the major features of 41 clinical studies of adverse psychological reactions are listed in Table 3. The following observations can be made:

(i) The total number of reported clinical cases, i.e., persons with adverse psychological reactions identified in treatment populations, is not very great (n = 426) for a drug which is as extensively used as cannabis. If the number of case reports is an accurate reflection of the incidence of such cases (which is not necessarily true), this appears to suggest that *serious* psychological disturbances from cannabis use are rare among users in general, without telling us just how rare.

(ii) A very high proportion of the reported cases come from the U.S.A. Some cases have been reported from Germany, France, Sweden, and England, but the non-U.S.A. cases represent only about 42% of the total. That cases from the U.S.A. are over-represented should be expected from the knowledge that rates of cannabis use and heavy use are much higher there than in other Western countries.

(iii) More psychological problems from cannabis have been reported for males than females; the ratio is about three males for one female, even when the survey studies with all-male military samples are deleted. The ratio of overall and daily use for males and females in the U.S.A., at least among young persons (from which most cases come), is about 1.5:1. There is a clear suggestion that female users are at lower risk than male users for serious psychological consequences of cannabis use. This may relate to their less frequent use of hallucinogenic drugs or to their tendency to use lower doses of cannabis even if they are daily users.

(iv) The mean age of the clinical cases is about 21. Very few cases are reported of people in their 30s, too few for real statistical inference. However, it does appear that older cannabis users (over 25) are under-represented among those with adverse reactions.

(v) Information on use of other drugs is frequently, but not always, reported in the clinical studies. It appears likely that 80% of clinical cases have used other hallucinogenic drugs. This percentage would be higher than among cannabis users in general, but probably not much higher than among heavy users who are not patients. However, the results of survey studies uniformly indicate that adverse reactions are more common among those who have used other hallucinogenic drugs. There is the suggestion of a "safe" dose in the Tennant and Groesbeck (1972) study, which showed that users taking less than 10–12 g hashish per month had no adverse effects other than minor respiratory problems. Of course, only psychological and not all physical adverse effects were examined in that study.

(vi) A few cases of adverse psychological effects have been reported among experimental and infrequent users (e.g., Keeler *et al.*, 1968; Perna, 1969; Smith, 1971). Since such users probably (but not necessarily) take rather small doses, it is possible that there is no totally safe dose of cannabis. However, more than 80% of cases involve heavy, or at least regular, cannabis users, although the criteria for defining the extent of use vary greatly from one study to another.

(vii) Information on other demographic or personality variables is not included often enough to permit any overall judgment about how they are related to the adverse reaction. A strong impression is gained that more than expected numbers of patients had previous psychological disturbances but the methods of assessing them vary

TABLE 3

Clinical Cases of Adverse Psychological Reactions to Cannabis (Psychoses, Flashbacks, Anxiety Reactions)

No. of Cases	Sex Ratio	Ages	Doses Used	Other Demographic Data	Adverse Reactions	Reference
4	3 males 1 female	18	Varied (single occasion to daily use)	—England —Two had family history of psychiatric problems and also used other drugs	—Hallucinations and paranoid delusions —Two overdose cases—both individuals were addicts —Vomiting and tremors	Baker and Lucas, 1969
1	male	30	1–2 marihuana cigarettes	—U.S.A. —Used for 1 yr prior to the episode (weekly then daily) —Middle-class background —Married —No family history of mental illness —College art graduate	—Visual hallucinations —Felt he was Christ and bound to die for the world —Had to be restrained from jumping out of a window	Bartolucci *et al.*, 1969
46	34 males 12 females	16–28		—Sweden —36 patients had sporadically used other drugs —For 16 patients psychosis preceded cannabis use	—24 psychotic episodes (1–5 wk) —22 psychotics (chronic)	Bernhardson and Gunne, 1972

4	3 males 1 female	19–22	Varied	—U.S.A. —Experienced and naive users —Students seen in mental hygiene service of university health department —Large, private eastern university —One was a previously diagnosed schizoid character	—Anxiety —Severe paranoid delusions and anxiety —Hallucinations of turning into a scary monster —Experienced and re-experienced perceptual distortions, paranoid ideation	Bialos, 1970
11	4 males 7 females	16–22	Regular users of cannabis but no other drugs	—Psychotic cannabis users —Canada	—10 of 11 had abnormal EEGs although only 2 had these prior to beginning use of cannabis	Campbell, 1971
46	All males			—U.S.A. servicemen in Vietnam —Psychiatric patients	—Prone to administrative difficulties (courts martial, etc.) —Statistically significantly more of this group than of general patients used marihuana	Casper *et al.*, 1968
4	All males	19–24	Casual to regular users	—Referred for psychological assessment in London, England —College or past college students —Used other drugs, particularly LSD	—Anxiety and unreality —Fear of losing sanity —Attempt to trepan own skull —Psychotic symptoms	Dally, 1967

TABLE 3 (CONTINUED)

No. of Cases	Sex Ratio	Ages	Doses Used	Other Demographic Data	Adverse Reactions	Reference
1	male	21	Regular user for 1 yr	—University student —Admitted to general psychiatric unit in Newcastle, England —Other drug use but not LSD	—Fear of homosexuality —Inability to concentrate on school work —Hallucinations and depression	Davison and Wilson, 1972
1	male	20	Smoked 5 "magic herb" cigarettes (cannabis)	—Paris —Left home because of non-compatibility with his step-father	—Thought he killed his father and surrendered to police, was not sure if it was a dream (as it was)	Delay, 1944
3	2 males 1 female	not specified		—Minimal use of other drugs —One had a history of mental illness —Sweden	—Schizophrenic symptoms including changes in perception and personality and thought aberrations	D'Elia *et al.*, 1970
1	male	18	Regular user	—College freshman, intelligent, middle-class background —LSD on one occasion —U.S.A.	—Recurrence of terrifying LSD reaction after smoking for the first time since the LSD reaction 3 mo previous	Favazza and Domino, 1969
1	male	39	Cannabis smoking occasionally	—Occasional excessive use of alcohol —Artist —London, England	—Acute confusion, thought disorder and hallucinations —Emotional incongruity and paranoid ideas	George, 1970

6	5 males 1 female	22–25	Variable amount and frequency of ganja and bhang use	—Westerners living in India	—Disorganized thoughts, anxiety, bizarre ideation, hyperactivity —Moderate anxiety reactions to psychotic reactions	Grossman, 1969
12	7 males 5 females	17–33	Varied	—Some used other drugs —Seeing psychiatrist for some reaction apparently related to cannabis use —U.S.A.	—Psychoses associated with organic brain syndromes (develops classification system de-emphasizing schizophrenic episodes)	Hart, 1976
87	Some males Some females		Excessive use of cannabis for 1–3 yr	—Germany —Frequent drug users. Out of 47 cases of flashbacks only 4 had never used LSD	—47 cases of flashbacks	Hasse and Waldmann, 1971
1	male	20	Heavy regular marihuana user for at least 6 mo	—American soldier in Vietnam	—Delusions, paranoid ideas, agitation, depersonalization	Heiman,
8	6 males 2 females		Chronic regular users of marihuana	—U.S.A. —All employed or students —Pre-existing psychotic disturbances	—Schizophrenic reactions —Delusions and hallucinations	Hekimian and Gershon, 1968
1	male	21	1. Ingestion of marihuana on 1 occasion 2. Ingestion of marihuana during 3-day episode	—User of both LSD and marihuana —U.S.A.	1. Acute paranoid schizophrenic reaction —Hallucinations 2. Semicomatose —Found to have diabetic ketoacidosis as a result of over-taxing metabolic system	Hughes *et al.*, 1970

TABLE 3 (CONTINUED)

No. of Cases	Sex Ratio	Ages	Doses Used	Other Demographic Data	Adverse Reactions	Reference
5			Recent marihuana smoking	—American college students	—A "high" state lasting from a few days to several months —Panic reactions, inability to concentrate, perceptual distortions	Janowitz, 1967
			Heavy users	—American soldiers stationed in Vietnam who were in- or out-patients at the 98th Medical Detachment	—Paranoid feeling and loss of reality (toxic psychoses) —Amotivational, irresponsible —Some remained schizophrenic	Kaplan, J.H., 1971
5	All females	16–27	Social doses of marihuana	—No previous history of psychiatric illness —U.S.A.	—Acute psychosis, perceptual distortions, hallucinations, paranoia, acute anxiety	Kaplan, H.S., 1971
11	6 males 5 females	19–23		—All university students or past students —Superior intelligence —U.S.A.	—4 cases of paranoia —2 cases of depression —1 case of depersonalization —1 case of confusion and disorientation —1 case of panic and fear	Keeler, 1967
4	All males	21–23	Multiple and single dose	—None had used other hallucinogens or showed evidence of serious psychopathology —U.S.A.	—Spontaneous recurrence of unusual visual or somatic sensations originally encountered during marihuana intoxication	Keeler *et al.*, 1968

14	12 males 2 females	17–33	Chronic users	—Case histories of patients admitted to “mental” hospital —Multiple long-term drug users —U.S.A.	—Flashbacks, acute paranoid reactions, psychosis, anxiety, confusion, irritability, hallucinations	Keup, 1970
1	male	26	Less than 2 marihuana cigarettes	—U.S.A. —Person had previously shown a high degree of tension but no history of psychiatric illness	—Psychotic reactions including delusions, auditory and visual hallucinations	Klee, 1969
38	20 males 18 females	13–24	2–3 times weekly	—heavy chronic users with psychiatric complaints —U.S.A.	—Psychosis, suicidal attempts, poor concentration and attention span, anxiety, apathy	Kolansky and Moore, 1971
13	9 males 4 females	20–41	At least 3 times a week for 16 mo	—Heavy chronic users with psychiatric complaints —U.S.A.	—Apathy, impaired short-term memory, disturbed sleep cycles	Kolansky and Moore, 1972
50		13–18	Heavy chronic users	—Outpatient psychiatric population —U.S.A.	—Impaired attention span, psychomotor depressant effect, inability to concentrate	Kornhaber, 1971
1	female	19	Regular and escalating hashish use for 2 yr (then also use of morphine)	—France	—Psychotic symptoms, atypical depressive syndrome, auditory hallucinations, increasingly autistic and hostile	Lelord and Stephant, 1972

TABLE 3 (CONTINUED)

No. of Cases	Sex Ratio	Ages	Doses Used	Other Demographic Data	Adverse Reactions	Reference
1	male	21	Smoked 70–80 times in his life, all pleasant episodes but the last	—College student referred to psychiatrist because of signs of panic reaction —Intelligent—academic family —U.S.A.	—Experienced extreme anxiety, required hospitalization and tranquilizers 1–2 days —Despite absence of drug use, anxiety remained for 7 mo	Marten, 1969
10	5 males 5 females	18–27		—Persons reporting adverse emotional reactions —Canada	—"Psychological vulnerability" most important in explaining likelihood of adverse psychological reactions in cannabis users	Negrete, 1973
1	male	23	Second experience with low dose	—A history of emotional problems but not psychotic —U.S.A.	—Extreme agitation and blocking of thought, ideas of reference, delusions, and confusion	Perna, 1969
1	female	17	1 yr of heavy use later mixed with opium use	—Germany	—Disruptions in concentration and thought processes, withdrawn, restless	Petri, 1970
3	2 males 1 female	17–20	Relatively small amount of hashish	—1 homosexual and 2 children of alcoholic fathers —Germany	—Psychoses disappeared when hashish was discontinued	Pietzcker, 1975

1	male	Started at 13	Heavy use (10–12 pipes daily for 6 days)	—France	—Catatonic state with little spontaneous movement or speech for 12 days —Recovered spontaneously, remembering nothing of the incident or period of hospitalization	Scouras, 1939
1	male	34	Low dose, first exposure	—U.S.A.	—Anxiety reaction	Smith, 1971
5	All males	18–22	—4 used twice a week for 1–2 yr with lesser involvement in more potent hallucinogens —1 used cannabis only for a continuous "stone" for several days	—University students who contacted student health services —Canada	—Apathy or lack of initiative	Thurlow, 1971
4	All males	18–24	All used marihuana heavily for some period of time, 2 used other drugs	—A suicidal man with a family history of mental illness, a marine who had used a variety of chemicals while overseas, a man who was hospitalized at age 15 for a severe schizophrenic illness, a man who had used psychedelic drugs on more than 100 occasions —U.S.A.	—Delusions, bizarre behavior, thought disorders, and agitation	Treffert, 1978

TABLE 3 (CONTINUED)

No. of Cases	Sex Ratio	Ages	Doses Used	Other Demographic Data	Adverse Reactions	Reference
1	male	27	Heavy user of drugs (including cannabis, and especially amphetamines) for more than 3 yr	—University student, ex-serviceman —U.S.A. into space, and grimacing	—Pseudocatatonia with mutism, decreased motor activity, negativism, staring	Warner and Pierozynski, 1977
2	males	College student and 30	1–6 uses	—College student and a college graduate —U.S.A.	—Flashbacks, including acute anxiety, depression, and fear of failure were reported 3 wk after using 6 times and 1 mo after the first use by the other individual	Wentworth-Rohr, 1970
16	males females (at least 2)	19–30	5 were one time or sporadic users and 11 were heavy long-term users most of whom used LSD sporadically	—Students, employed and unemployed —U.S.A.	—4 cases of massive anxiety, 2 cases developed schizophrenia, 2 cases of suicidal depression, 6 cases of manifest disorders of thought and concentration of nonschizophrenic nature, and 2 cases of marked conceptual, attentional, and perceptual disruptions	Wurmser *et al.*, 1969

greatly. The expected rate of such disturbances in the population from which the cases are drawn is often uncertain.

In summary, it appears likely that minor adverse reactions to cannabis, especially of a psychological nature, are common among users. Serious reactions requiring treatment probably are not common, although their real frequency is not as well known for users in general as it is for heavy-using groups. The high-risk users for such reactions would appear to be males, young persons, users of other hallucinogenic drugs, and probably those with pre-existing psychological problems.

7. NEEDS FOR FURTHER RESEARCH

In general it appears that the epidemiology of cannabis use and the clinical epidemiology of adverse reactions are fields that have grown up separately. Those who study rates of use in general populations rarely take an interest in adverse reactions of a serious nature, i.e., those requiring treatment. The frequency of cannabis use in general populations and its correlates appear to be better known than are rates of adverse reactions and their correlates. The major needs for further epidemiological research are:

(i) Continued monitoring of trends in cannabis use in general populations, with more use of longitudinal studies of cohorts beginning in teenage years and continuing at least until the age of 50 or 60 yr.

(ii) More study of the frequencies of all types of adverse reactions, especially those requiring treatment, in surveys of cannabis users. An effort should be made here to separate the influence of various factors such as dose, frequency of use, experience with other drugs, and pre-existing psychopathology. Surveys in adult populations are particularly necessary since all previous investigators have studied primarily students. There is also a special need for studies of the frequency of respiratory, hormonal, cardiovascular, and other nonpsychological adverse consequences of cannabis use.

(iii) More attention in cannabis studies (e.g., of changes in sexual and endocrine function and cardiovascular problems) to the identification of both the rate of serious problems and the characteristics of those at high risk. To do this may necessitate an increase in the sizes of samples being studied and a broader sampling of the total population using cannabis.

(iv) More effort, in retrospective studies of clinically identified adverse reactions, to utilize control or comparison groups so that the *apparent* over-representation of certain characteristics (e.g., age, sex, previous drug use, pre-existing psychological problems) could be assessed.

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